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# *The electroencephalogram in neonatal convulsions*

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IN 1937 J. Roy Smith[34] reported on the electroencephalogram (E.E.G.) in infancy and childhood and included a description of the essential features of the E.E.G. of newborn babies and the differences between the waking and sleeping records. Since then there have been extensive studies in various centers and progress has been made in correlating the E.E.G. with maturity and the physiologic state. The contributions of Schroeder and Heckel,[31, 32, 33] Brown and Hughes,[12-17] Dreyfus-Brisac and her colleagues,[3-7] Kellaway,[19, 20] Imperato and Landucci,[18] and Ellingson[8] are of special interest. Many investigators have shown that clearly recognizable abnormalities can be detected in the E.E.G.'s of ill, newborn babies, especially those with convulsions, but attempts to analyze the significance of the abnormal E.E.G. in terms of clinical state and progress have been relatively few.

There are a number of questions concerning the clinical use of the E.E.G. in the newborn which should be clearly stated even if they cannot be clearly answered: (1) What constitutes an abnormal E.E.G. in the newborn? (2) Is an abnormal E.E.G. invariably accompanied by an abnormal clinical state, and vice versa? (3) How *often* are E.E.G. abnormalities found when recordings are made both during and between convulsions? (4) Is the E.E.G. of any value as a guide to treatment or prognosis?

This paper describes a study of the E.E.G. in 41 babies who developed convulsions in the neonatal period. An attempt has been made to classify the E.E.G. abnormalities found, and to relate them to the type of con-

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**Table I**

| *Serial number* | *Birth weight in grams* | *Age in days at onset of fits* | *When fits continued, age in days at last fit* | *Clinical associations* | *Type of fits* |
|---|---|---|---|---|---|
| 21 | 2,600 | 6 | | | Cyanosis and tonic spasms |
| 40 | 3,940 | 4 | 10 | Intracranial hemorrhage | Tonic spasm; pallor; "warding-off" movements; general jerking |
| 41 | 2,860 | 2 | 2 years old | Sibling 1. Possible metabolic disorder | Tonic spasms; generalized clonic jerking |
| 45 | 1,380 | 1 | 3 | Perinatal anoxia | Tonic spasms after apnea |
| 51 | 3,560 | 2 | | | Tonic spasm |
| 52 | 1,540 | 2 | 3 | Congenital heart disease | Tonic spasm |
| 61 | 3,180 | 1 | 5 | Obstetric trauma; perinatal anoxia | Generalized tonic clonic spasms; eyes rolling |
| 62 | 3,080 | 1 | | Perinatal anoxia | Tonic spasms; "warding-off" movements |
| 72 | 3,320 | 8 | 10 | Obstetric trauma | Multifocal jerking |
| 78 | 1,540 | 3 | | Maternal toxemia | Multifocal jerking |
| 85 | 2,860 | 1 | 7 | Perinatal anoxia; maternal toxemia | Tonic generalized clonic |
| 109 | 3,080 | 2 | 7 | Family history of fits | Multifocal jerking |
| 110 | 2,940 | 6 | | | Tonic spasm; multifocal clonic |
| 111 | 4,480 | 6 | 10 | | Multifocal jerking |
| 127 | 2,360 | 12 | 19 | Cerebral malformation | Generalized tonic clonic |
| 128 | 3,340 | 1 | 2 | Obstetric trauma; perinatal anoxia | Tonic spasm; generalized clonic |
| 132 | 4,060 | 1 | 2 | Perinatal anoxia | Hypertonic flexion spasm |
| 140 | 2,920 | 2 | 4 | Perinatal anoxia | Tonic spasm; multifocal jerking |
| 144 | 2,540 | 1 | | Perinatal anoxia | Tonic spasm |
| 145 | 3,320 | 5 | 6 | | Tonic spasm; multifocal clonic |
| 146 | 1,720 | 2 | | Perinatal anoxia | Tonic spasm; multifocal jerking |
| 147 | 3,940 | 1 | 7 | Perinatal anoxia | Tonic spasm; multifocal jerking |
| 148 | 1,760 | 3 | 6 | Maternal toxemia; hypoglycemia | Tonic spasm; multifocal jerking; "warding-off" movements |
| 149 | 2,180 | 1 | 9 | Perinatal anoxia; hypoglycemia | Tonic spasm; general tremor; eyes staring; "warding-off" movements |
| 159 | 3,280 | 2 | | Perinatal anoxia | Multifocal clonic; pallor; eyes staring |

| Seizure E.E.G. | Inter-seizure E.E.G. | Outcome | Age (years, months) |
|---|---|---|---|
| | Bilateral focal sharp waves | Normal | 2 9 |
| | Bilateral focal sharp waves plus focal slow and sharp wave complex | Fit at 3 years Normal development | 3 0 |
| Bilateral small amplitude | High amplitude multifocal spikes | Fits; mental retardation; death | 2 0 |
| Bilateral small amplitude | Bilateral small amplitude | Death | 3 days |
| | Normal | Not followed | |
| | Bilateral small amplitude | Death | 4 days |
| Bilateral small amplitude; plus generalized "episodic sleep activity" like bursts | General rhythmic 1 c/s | Spastic diplegia | 3 0 |
| Muscle artefact | Bilateral sharp waves | Mental retardation | 3 0 |
| Movement artefact | Unilateral rhythmic 10 c/s slowing to 2.5 c/s before onset of fit. Otherwise normal | Normal | 1 0 |
| Bilateral rhythmic 1.3 c/s | Bilateral small amplitude | Death | 4 days |
| Bilateral small amplitude | Normal | Normal | 1 7 |
| | Normal | Not followed | |
| | Normal | Normal | 2 0 |
| | Unilateral sharp waves | Normal | 1 6 |
| Bilateral small amplitude | Rhythmic focal 8 c/s. Bilateral rhythmic 1.3 c/s | Death | 19 days |
| | Rhythmic unilateral 4 to 5 c/s on fifth day. Normal after fit | Normal | 1 9 |
| | Normal | Normal | 1 0 |
| | High amplitude unilateral sharp waves | Normal | 1 4 |
| | Bilateral focal sharp waves | Normal | 1 6 |
| | Unilateral high amplitude focal sharp waves | Normal | 1 6 |
| | Bilateral small amplitude | Death | 3 days |
| Bilateral small amplitude or no change | Bilateral focal sharp waves | Mental retardation | 1 0 |
| Bilateral focal repeating slow and sharp wave complex lasting 0.2 to 0.4 second | Bilateral small amplitude | Mental retardation | 1 6 |
| | Sharp waves in episodic sleep activity; bilateral sharp waves | Spastic diplegia; fits; mental retardation | 1 3 |
| Unifocal slow and sharp wave complex 2 to 3 a second | Unilateral wave complex or normal | Normal | 1 0 |

**Table I.** Cont'd

| *Serial number* | *Birth weight in grams* | *Age in days at onset of fits* | *When fits continued, age in days at last fit* | *Clinical associations* | *Type of fits* |
|---|---|---|---|---|---|
| 163 | 1,840 | 17 | 19 | Intracranial hemorrhage | Tonic spasm; multifocal jerking; "warding-off" movements |
| 168 | 2,220 | 2 | 9 | Maternal toxemia; perinatal anoxia; hypoglycemia | Tonic spasm; staring eyes; general jerkiness |
| 170 | 1,700 | 2 | | Maternal toxemia; perinatal anoxia; hypoglycemia | Generalized jerking; eyes rolling |
| 173 | 2,240 | 3 | | Perinatal anoxia | Tonic spasm; focal jerking |
| 175 | 1,380 | 2 | 4 | Maternal toxemia; perinatal anoxia; hypoglycemia | Tonic spasm; generalized jerking; eyes staring and rolling |
| 182 | 1,840 | 2 | 12 | Cerebellar cysts | Hypotonia; pallor; multifocal jerking |
| 197 | 3,520 | 1 | To present age, 1 year | Cerebral malformation | Brief generalized jerk |
| 203 | 2,780 | 1 | | | Focal jerking |
| 206 | 3,000 | 1 | 3 | Perinatal anoxia | Tonic spasms; multifocal jerking |
| 216 | 3,280 | 3 | 6 | Hemorrhagic disease | Tonic spasms; focal clonic |
| 217 | 3,200 | 1 | To present age, 4 months | Sibling 2. Possible metabolic disorder | Tonic spasms; generalized clonic |
| 222 | 2,240 | 1 | | Cerebral malformation | Tonic spasm |
| 225 | 4,080 | 2 | 5 | Intracranial hemorrhage | Tonic spasm; multifocal clonic |
| 231 | 1,360 | 3 | 4 | Hypoglycemia | Staring; pallor; multifocal jerking |
| 237 | 2,700 | 6 | 7 | Obstetric trauma | Focal jerking |
| 238 | 2,337 | 1 | 3 | Perinatal anoxia | Multifocal jerking; tonic spasm after apnea |

vulsion observed and to the clinical state and the progress of the babies.

## SUMMARY OF PUBLISHED WORK

The following is a summary of the reported work concerning abnormal E.E.G.'s in the newborn.

Sureau, Fischgold, and Capdevielle[35] in 1950 studied the E.E.G. of babies who had been subjected to obvious obstetric trauma or who showed clinical signs of cerebral disorder and reported a variety of E.E.G. abnormalities. Schroeder and Heckel[32] in 1953 described 6 cases in detail and reported in general terms on a follow-up examination of 55 clinically or electroencephalographically abnormal newborn babies. Fischgold and Berthault[10] in the same year concluded that the tracing of the newborn baby was the same when the birth had been normal or

| Seizure E.E.G. | Inter-seizure E.E.G. | Outcome | Age (years, months) |
|---|---|---|---|
| | Bilateral small amplitude; some rhythmic bilateral 8 c/s | Death | 23 days |
| | Rhythmic 14 to 20 c/s; bilateral focal sharp waves | Fit at 10 months | 1 0 |
| Bilateral small amplitude | Bilateral small amplitude | Normal | 5 |
| | Bilateral small amplitude | Normal | 3 |
| | Rhythmic 12 to 14 c/s | Normal | 5 |
| Jerks followed by "episodic sleep activity" | Normal | Death | 12 days |
| | Bilateral small amplitude | Fits; mental retardation | 1 0 |
| | Normal | Normal | 6 |
| Bilateral rhythmic 1.3 to 2 c/s and focal sharp wave complex | Bilateral small amplitude | Normal | 6 |
| Unifocal complex of 2 to 3 sharp waves at 2 bursts per second to 1 burst every 2 seconds | Unilateral rhythmic 2 to 5 c/s plus sharp wave complex | Fit at 11 months<br>Normal | 1 5 |
| Bilateral small amplitude | Multifocal high amplitude spikes | Fits | 4 |
| | Normal | Death | 5 days |
| Bilateral small amplitude or bilateral rhythmic 2 c/s plus sharp wave complex | Normal or bilateral or focal wave complex | Normal | 3 |
| Bilateral slow and sharp wave complex recurring at 1.3 c/s | Normal | Normal | 1 |
| | Normal | Not followed | |
| | Normal | Not followed | |

when complicated by anoxia or severe cerebral lesions, but this appears to be based on some observations of Madame Arfel Capdevielle on 20 newborn babies, only 4 of whom suffered from fits. In 5 examined personally by Fischgold and Berthault after the early neonatal period they concluded that recordings during convulsions were characterized by sharp wave discharges, local or generalized, but slower than those seen in older children or adults. Minkowski[26] and his colleagues found paroxysmal features in the E.E.G.'s of 3 infants recorded during fits, but did not find characteristic changes in records from newborn babies a few days after fits. The most comprehensive paper is that of Ribstein and Walter[29] who studied 75 cases of convulsions in babies from birth to 45 days of age. They were able to obtain 50 records in 9 babies during fits and these

showed focal discharges. Twenty-five per cent of their ill babies had normal interseizure records and many others had only doubtfully abnormal records. Their discussion on the focal nature of neonatal fits is based on these findings and they conclude that the immature neonatal brain is incapable of developing a complete epileptic fit either functionally or electrically. In a report to the E.E.G. Society meeting in 1958 Cadhilac, Passouant, and Ribstein[1] expanded these observations with a study of 90 babies who had convulsions between birth and the age of 6 weeks. They exphasize that the discharges are focal, starting with slow waves or rapid spikes, and that their propagation is restricted either to one hemisphere or to the symmetrical region of the contralateral hemisphere. They made recordings during 60 fits and found no generalized and synchronous abnormalities. They found 2 or more different foci in over half their patients. More than 20 per cent of their patients died and another 20 per cent showed evidence of neuropsychiatric sequels at one year, even though the convulsions had disappeared within a few days of the onset.

In a long paper on the E.E.G. of the infant, Imperato and Landucci[18] comment on 3 types of electrical activity seen in newborn babies with cerebral disturbances but never in the normal newborn. These are (1) "spikes" which are much slower than those of the older child or adult, (2) paroxysmal irregular slow activity of high voltage on a flat background and (3) fast activity. They comment on the diagnostic value of the E.E.G. of the newborn in distinguishing between fits and apneic attacks and suggest that it may also help to differentiate a reversible condition such as edema from intracranial hemorrhage and thus be of value in prognosis.

## PRESENT INVESTIGATION

**Material.** Forty-one babies have been observed during the acute stage of the convulsive illness; 7 of them died in the early neonatal period. Of the survivors it has been possible to follow the progress of 31 for a year or more (see Table I). The oldest ones in the series are now in their fourth year. It was not usually possible to arrive at an exact diagnosis of the primary condition underlying the convulsive state. Certain clinical correlations could be made but in some cases the cause of the fits was obscure.

**Technique.** Recording the E.E.G. in the neonatal period was carried out by a standardized method using 6 chlorided silver cup electrodes placed equidistantly around the head, one frontal, one occipital, and 2 on either side to straddle the motor cortex. The electrodes were held in place by a cap of

**Table II.** Day of life on which first fit occurred

| Day of life | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12+ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No. of babies | 15 | 12 | 5 | 1 | 1 | 4 | 0 | 1 | 0 | 0 | 0 | 2 |

**Table III.** Clinical associations in neonatal fits*

| | *Premature* | *Full term* |
|---|---|---|
| Obstetric trauma | 0 | 4 |
| Perinatal anoxia | 8 (1) | 10 (1) |
| Hypoglycemia | 6 (4) | 0 |
| Known intracranial hemorrhage | 1 | 2 |
| Hemorrhagic disease of the newborn | 0 | 1 |
| Cerebral malformations | 3 | 1 |
| Inherited metabolic defect? | 0 | 2 |
| Family history of fits | 0 | 1 |
| Congenital heart disease | 1 | 0 |
| No known clinical association | 1 (1) | 7 |

*Six of the 41 babies appear twice in this table: 4 premature babies suffered from perinatal anoxia and hypoglycemia; 2 babies who underwent birth trauma also suffered perinatal anoxia.

The figures in brackets refer to numbers of babies in each category whose mothers had pre-eclamptic toxemia in this case defined as hypertension of 140/90 or more *and* albuminuria. There is a total of 6 such babies (one suffered both from anoxia and hypoglycemia) out of the total of 41 with fits. In the 3 years 1956 to 1958, 269 out of 6,633 mothers delivered at the Hammersmith Hospital had pre-eclamptic toxemia as defined above. Calculating from the 2 × 2 contingency tables (Finney, 1948) $\chi^2 = 11.06$ $P = < 0.001$. This should be regarded as highly suggestive rather than a statistically significant finding of an association between maternal toxemia and neonatal fits, because the exact number of cases of neonatal fits in the total population of mothers with and without toxemia is not known.

elastic mesh, the underlying skin was prepared with acetone, and chloride electrode jelly was applied. Recording was scalp to scalp from adjacent pairs of electrodes longitudinally in the anteroposterior line. The E.C.G. and respiration were also recorded. An 8-channel Ediswan Mark II encephalograph was used. The technique is easy and can be carried out, even if the baby is in an incubator, without much disturbance to the baby or to nursing procedures. When possible recordings were made during fits; otherwise the first recording was carried out within 24 hours of the onset of symptoms. Records were repeated until recovery from the acute illness and thereafter when the baby was seen for examination at the follow-up clinic.

**Clinical description of convulsions.** Table II shows the day of life in which fits occurred for the first time; it is, of course, possible that the first fit or fits were not always observed. Table III lists the clinical conditions associated with fits in these babies.

Walter and Ribstein[29] state that fits in the neonatal period are nearly always "symptomatic" rather than "idiopathic." All but one of their 75 infants had suffered some complication of birth or some neonatal illness, which might have accounted for the fits. The 41 cases here reported tend to confirm the observation of Walter and Ribstein but it is seldom possible to assign a wholly satisfactory cause for the fits. Even severe obstetric trauma is not necessarily complicated by neonatal fits. In any case only 4 of the 41 cases could be assigned to this cause. Perinatal anoxia, as evidenced by changes in fetal heart rate, meconium-stained liquor amnii, difficulties in initiating respiration at birth, and apneic attacks in premature babies, may all occur without apparently provoking fits. All the cases of hypoglycemia* were of small premature babies. It is known that newborn babies are highly resistant to low blood sugars, but adequate controls for this series are not available. The cause of the undoubted intracranial hemorrhages which occurred on the third day in 2 infants who survived is unknown. One baby had hemorrhagic disease of the newborn, and intracranial hemorrhage was suspected, but not confirmed. In 8 cases the onset of fits was entirely unexpected and there was no obvious cause. It is of interest that 6 of the mothers of these babies suffered from pre-eclamptic toxemia, but in 4 cases their babies were born prematurely. The following cases are of special interest from the medical standpoint.

**Possible inherited metabolic defect.** *Case 41.* There was an uncomplicated breech delivery at term of a male infant who appeared normal until the third day when fits were first observed. These were generalized tonic spasms with apnea, sometimes followed by symmetrical clonic movements of all limbs and often ending with a loud cry. These fits became very frequent, more than 12 a day, in spite of anticonvulsant drugs. The number of fits decreased when he was 5 months old and thereafter were only occasional. There was never any mental or motor development and he died at 2 years of age of pneumonia in an institution. Investigations during life did not indicate any anatomic or metabolic abnormality. No autopsy was performed.

*Case 217, Sister of Patient 41.* There was a spontaneous vertex delivery at term. She appeared normal at birth but fits were first observed 8 hours after delivery. These fits were similar to those suffered by the first baby and were very frequent, often 2 or 3 in an hour, and did not begin to decrease in frequency until 3½ months, in spite of the trial of many anticonvulsant drugs. An attempt to control fits with prednisone failed, as did a trial with pyridoxine. An intravenous injection of pyridoxine during a recording did not bring about any improvement in the E.E.G. tracing. There was no evidence of aminoaciduria, phenylketonuria, hypoglycemia, maple sugar disease, or other recognized metabolic defect or anatomic defect. At 4 months of age the baby shows no evidence of motor or mental development.

*At least 1 blood sugar estimation of less than 20 mg. per 100 ml.

The parents of these babies are first cousins. There is no family history of mental defect or epilepsy. The E.E.G.'s of both children were identical, and nothing resembling them has been seen in any other case of neonatal fits. In the neonatal period they consisted of long bursts of almost continuous large amplitude, multifocal spikes, and irregular high voltage slow wave activity (Figs. 1 and 2). In between these episodes the record was relatively flat.

**Possible inherited anatomical defect.** *Case 182.* The mother had had 3 previous normal pregnancies with delivery of normal healthy girls, by a previous marriage. This baby, the first child of her second marriage, was delivered at term; the birth weight was 1,840 grams. He was normal at birth but on the second day had an attack of limpness, pallor and jerky limb movements with twitching of the left corner of the mouth at the onset of the attack. The baby then became increasingly hypertonic and had further fits of the multifocal clonic variety. On the twelfth day the baby collapsed after a fit and died. At autopsy bilateral subarachnoid cysts were found overlying the posterior poles of each cerebellar hemisphere. A second male child delivered normally at term, apparently healthy at birth, died suddenly on the third day, and at post mortem was found to have an exactly similar abnormality.

E.E.G. of the first baby showed little abnormality. The background activity was flat. Immediately following generalized twitching there was a burst of activity resembling

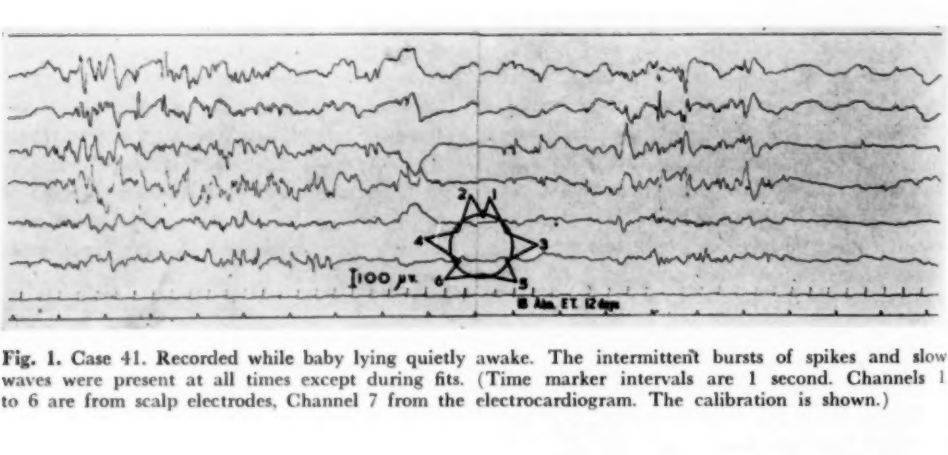


**Fig. 1.** Case 41. Recorded while baby lying quietly awake. The intermittent bursts of spikes and slow waves were present at all times except during fits. (Time marker intervals are 1 second. Channels 1 to 6 are from scalp electrodes, Channel 7 from the electrocardiogram. The calibration is shown.)

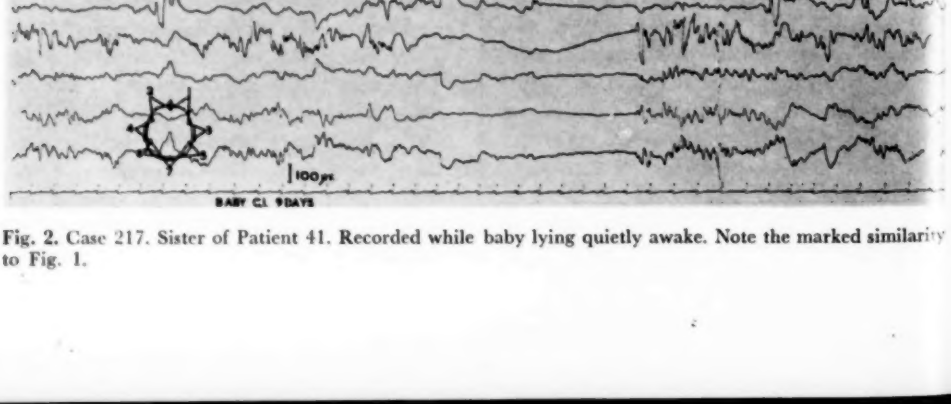


**Fig. 2.** Case 217. Sister of Patient 41. Recorded while baby lying quietly awake. Note the marked similarity to Fig. 1.

the episodic activity occurring spontaneously or after arousal stimuli during sleep in normal full-term infants, but in this baby containing sharper elements than normal. No E.E.G. examination was performed on the second baby.

**Type of convulsions observed.** The recognition of fits in the newborn is not always easy. For instance, attacks of apnea are sometimes difficult to interpret. A sudden cessation of respiration may be the first manifestation of a generalized tonic fit. On the other hand, intermittent apneic attacks in premature infants, which are prolonged for several minutes, may terminate in a tonic or tonic clonic fit. In the latter case it is reasonable to suppose that the fit has followed anoxia rather than that the anoxia has been an expression of the fit. Sudden jerks of the whole body are difficult to distinguish from mass reflexes. Excessive "jitteryness" in a premature baby is also difficult to interpret. In our cases episodes which were easily recognizable on clinical grounds as fits were mainly of 2 types.

*1. Tonic fits.* These appeared as attacks of apnea accompanied by simultaneous symmetrical tonic muscular contraction, characteristically leading to opisthotonos, extension of arms and thighs, flexion of forearms, and clenching of fists. This was sometimes preceded or followed by brief generalized clonic movements, but the classical major fit of older children and adults was rarely seen.*

2. *Focal fits.* These took the form of localized jerking at irregular intervals or rhythmic clonic movements, e.g., nystagmus to one side, twitching of one corner of the mouth, jerking or clonus of arm or leg. In one case Jacksonian progression of clonic movements was observed, starting with lateral movements of the eyes, then to face, hand, upper arm, shoulder, trunk, and leg on one side, and finally including the opposite limbs and trunk. When focal fits were repeated, the same limb might be involved, but in several cases localized clonic movements began at other sites. Breathing and color were usually maintained. In some babies both generalized tonic and focal clonic fits were seen at dif-

*The only really clear-cut examples of classical major fits occurred in the 2 siblings who suffered from an apparently inherited convulsive disorder and who are described above.

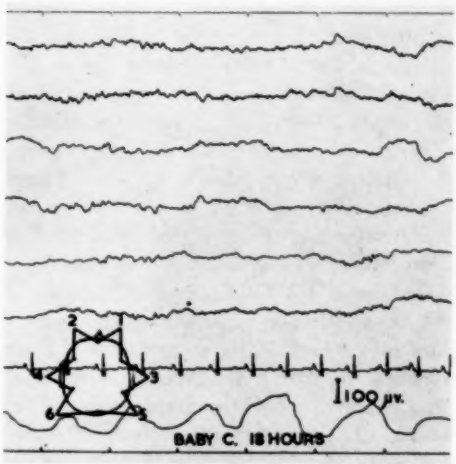


**Fig. 3.** Normal full-time baby lying quietly awake. (The first 7 channels are as in Fig. 1 and Channel 8 is the pneumogram. This is the usual recording plan.) This shows the generally symmetrical but arhythmic nature of the E.E.G.

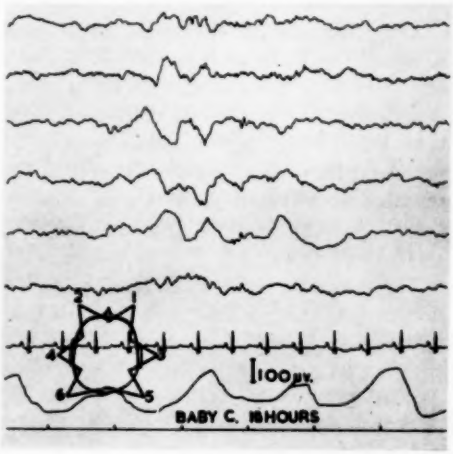


**Fig. 4.** The same normal full-time baby as in Fig. 3. Recorded during sleep. It shows a burst of larger amplitude activity. This type of activity recurs at intervals of several seconds in the record of normal-sleeping full-time babies.

ferent times. In 2 babies, fits took the form of attacks of staring, pallor, and generalized hypotonia. In between fits some babies displayed other manifestations symptomatic of cerebral disorders, such as excessive lethargy or irritability and depression of automatisms. Five babies with tonic fits, including 3 who also had focal clonic attacks, showed in between fits continuous vigorous alternating "warding off" movements of the arms.

**Abnormal E.E.G. findings.** Although the E.E.G. of the normal newborn and premature infant has clearly recognizable characteristics, a precise description is difficult. The record is mainly arrhythmic and varies according to the maturity and state of wakefulness or sleep of the baby (Figs. 3 and 4). The features of the normal neonatal E.E.G. have been discussed by several authors and it is hoped to add to these descriptions elsewhere. It is easier, though less satisfactory scientifically, to pick out activity considered abnormal on the basis of its correlation with the clinical state.

The following list represents an attempt to classify types of activity seen in E.E.G.'s of babies with fits and not, in the authors' experience, in the records of normal newborn babies: (1) rhythmic slow waves, (2) persistent focal sharp waves, (3) spikes, (4) repeated stereotyped sharp waves or wave complexes, (5) gross asymmetry, and (6) small amplitude.

The following types may possibly be abnormal, but are less easy to distinguish from activity seen in records of normal babies: (7) sharp waves during episodic sleep activity and (8) fast activity.

1. **Rhythmic slow waves.** These are never seen in the normal neonatal E.E.G. A normal baby just before going to sleep will sometimes show runs of slow waves for 2 or 3 seconds at about 1 to 2 cycles per second over the central areas. This activity is symmetrical and not rhythmic and is not likely to be confused with abnormal activity. The frequency of the abnormal activity is usually 1 to 2 cycles per second but may be faster up to 4 cycles per second or slower. The amplitude is in the order of 50 to 200 $\mu$V. It occurs in long runs, unilateral focal or generalized, both during and between fits (Figs. 5 and 6). A characteristic happening is of unilateral focal slow waves at, say, 3 cycles per second and 75 $\mu$V. amplitude at the onset of a fit, gradually developing into bilateral generalized rhythmic activity at, say, 1.5 c/s and 200 $\mu$V. amplitude during the fit. The association of slow waves with sharp waves to form repeating complexes is referred to below.

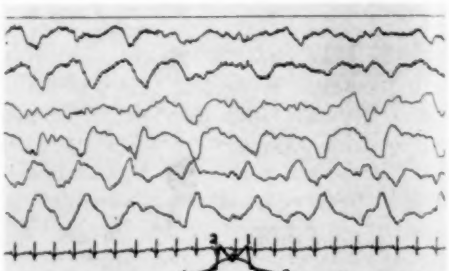


**Fig. 5. Case 61. This shows bilateral slow waves of great amplitude and several examples of such activity occurred in this baby, usually at the end of prolonged generalized tonic fits when the baby was still apneic.**

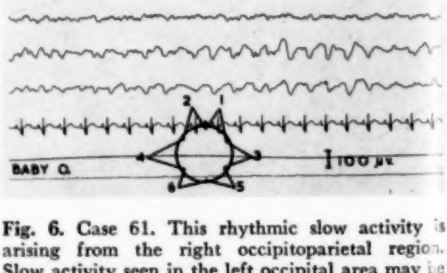


**Fig. 6. Case 61. This rhythmic slow activity is arising from the right occipitoparietal region. Slow activity seen in the left occipital area may be due to a common central occipital electrode. This was recorded from the same baby as shown in Fig. 5 before the onset of a clinical fit and while the baby lay quietly but had started an attack of apnea.**

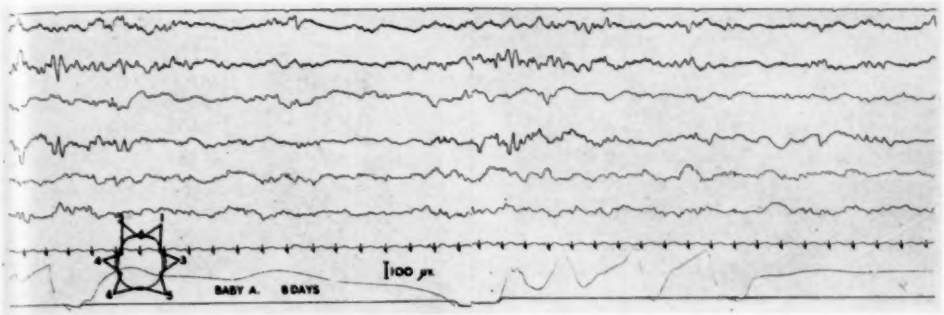


Fig. 7. Case 111. An example of persistent focal sharp waves seen repeatedly in the interseizure record of a baby who had multifocal jerking movements.

2. **Persistent focal sharp waves.** Occasional focal sharp waves of, say, 100 msec. duration and 75 μV. amplitude are not uncommonly seen in the records of clinically normal newborn babies when asleep. Sharp waves are reported as a frequent normal occurrence by authors from other European countries but the term "sharp wave" is applied more as a result of visual impression than as a scientific definition, and the slower paper speeds conventionally used in other countries may account for this difference. Focal sharp waves in convulsing newborn babies are characterized by their persistence and sometimes rhythmicity and differ from those seen in older children and adults by their extremely long duration (up to ½ second) and great amplitude (up to 300 μV.) (Figs. 7, 8, and 9).

3. **Spikes.** Again, it is difficult to make a valid distinction between spikes and sharp waves, but if one accepts that the duration of the former is 60 msec. or less, one can say that spikes are rare in the E.E.G. of newborn babies. In this series spikes have been seen only in 2 abnormal babies, the siblings referred to above, but in these 2 babies persistently.

4. **Repeated stereotyped sharp waves or wave complexes.** These are dramatic in appearance and never seen in the normal baby's record at any time. The complex may vary in the same baby during a single recording. The simplest form is a pair of focal sharp waves regularly recurring (Fig. 10), the frequency usually slowing toward the end of the burst. The rate varies from 2 to 3 complexes a second to one every 2 to 3 seconds, the whole burst continuing sometimes for several minutes. More complicated forms are seen consisting of an alternating slow wave and one or more mono- or multiphasic sharp waves. This activity is often of great amplitude. The form of the complex often develops during a burst from a small amplitude repeating single sharp wave to the complicated wave complex, spreading from one area to involve the whole of one hemisphere (Figs. 11-14) and then becoming generalized, although one hemisphere usually shows the abnormality more clearly. This activity, like rhythmic slow waves, may occur in the waking state or in sleep, between fits or during fits, and is especially associated with focal clonic fits.

5. **Gross asymmetry.** The impression given by a 10-second strip of a normal record is of general bilateral symmetry of wave frequency and amplitude, although there may be runs lasting a few seconds of asymmetrical activity at first on one, then on the other, side. Persistent asymmetry and amplitude has been reported in cases of acute subdural hematoma, but no proved case of subdural hematoma was examined in this series. Gross asymmetry observed has been mostly in cases of unilateral epileptic activity referred to above, but Fig. 15 shows absence of electrical

activity from one side of the head in a case of gross porencephaly (not included in this series as the baby did not suffer from fits in the neonatal period) (Figs. 16 and 17).

6. **Small amplitude.** Small amplitude is here defined as persistent activity below 50 $\mu$V. Even in babies of only 26 weeks' gestation there are bursts of electrical activity at greater amplitude, although the background may be extremely flat. In full-term babies, however, some of the background activity is always of greater amplitude than 50 $\mu$V. Small amplitude has been seen most frequently in ill, immature infants during periods of apnea, but also in some cases of generalized tonic fits in both immature and term babies (Fig. 18). Generalized flattening has been seen in 1 case of gross porencephaly with fits (Fig. 19) and in 1 case of congenital methemoglobinemia with mental defect.

7. **Sharp waves during episodic sleep activity.** Sleep records of normal full-time babies are characterized by bursts of higher amplitude activity at all wave frequencies occurring at intervals of several seconds.

One is on less certain ground in asserting that sharper elements seen in episodic sleep activity represent an abnormality, although this is so regarded by some authors. However, it is often seen in the E.E.G. records of babies showing other clear evidence of abnormal electrical activity.

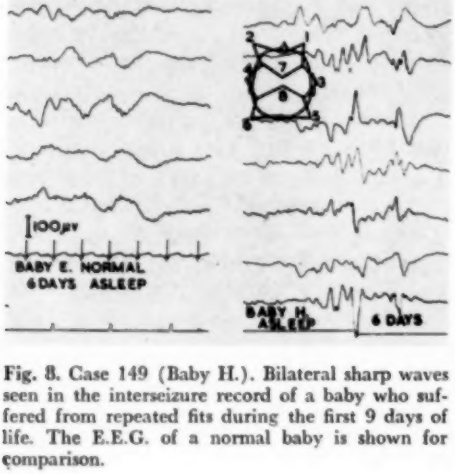


**Fig. 8.** Case 149 (Baby H.). Bilateral sharp waves seen in the interseizure record of a baby who suffered from repeated fits during the first 9 days of life. The E.E.G. of a normal baby is shown for comparison.

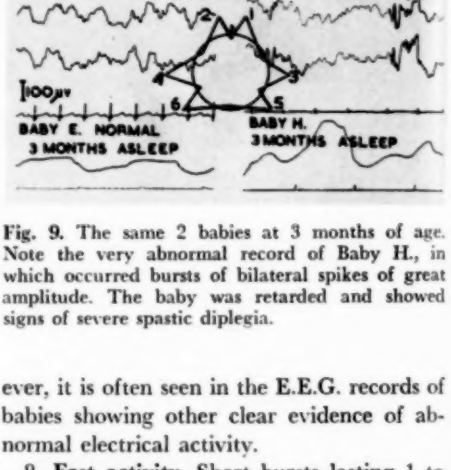


**Fig. 9.** The same 2 babies at 3 months of age. Note the very abnormal record of Baby H., in which occurred bursts of bilateral spikes of great amplitude. The baby was retarded and showed signs of severe spastic diplegia.

8. **Fast activity.** Short bursts lasting 1 to 2 seconds of rhythmic fast activity (14 to 20 cycles per second) are seen frequently in the record of immature babies and sometimes in healthy babies at term. Persistent generalized fast activity has been seen in a number of newborn babies, particularly when blood glucose levels were low (less than 15 mgm. per 100 ml.) (Fig. 20), but a clear association between fast activity and hypoglycemia has not been found. In one case of hypoglycemia intravenous infusion of glucose during an E.E.G. recording produced no definite change in the record.

In a case of cerebral malformation there were bursts of clearly defined rhythmic high potential 8 cycle per second activity showing phase reversal in the right frontal region (Fig. 21). This baby died and was found to have fusion of the cerebral hemispheres and absence of the corpus callosum.

A few commonly observed artefacts may be misleading. The E.C.G. may be seen; this can be confirmed by timing with the E.C.G. recorded from limb leads and is usually removed by reapplication of the electrodes to

improve contact. Small body movements may lead to spikes or sharp waves, usually in all channels; these are confirmed by observation of the baby during recording and often by the occurrence simultaneously on the E.C.G. of a similar artefact. Unilateral rhythmic slow activity of great amplitude may be seen due to body movement associated with respiration or strong sucking movements (Figs. 22 and 23). This is seen in the leads from the side of the head on which the baby lies and again is confirmed by observation and, in the case of respiratory artefact, by timing with the respiration record, and can be abolished by altering the baby's position.

**E.E.G. during fits.** Twenty-four recordings during fits were obtained from 18 of the babies. Five babies with localized clonic fits showed repeated focal stereotyped complexes in the E.E.G., coinciding in time with observed clonic movements. These complexes arose from the contralateral hemisphere but in some cases less striking abnormalities were seen arising from the ipsilateral hemisphere. Timing could be confirmed by simultaneous recording of a myogram from the affected part. Eight babies with tonic fits, with or without generalized twitching or clonic movements, showed only flattening of the E.E.G. during fits. This flattening might occur in a previously normal record or one which showed spikes, sharp waves, or rhythmic slow waves in the interseizure record. In the case of fits supervening during periods of apnea in premature infants, the record might already be flat (possibly as the result of cerebral anoxia) and therefore show no change. In a few cases the main feature of the record during fits was movement or muscle artefact. One baby who had very brief generalized repeated twitches showed bursts of activity, immediately following the twitches, which were similar to those bursts occurring spontaneously during normal sleep but which comprised sharper activity than usual. There seems to be a fairly constant relationship between the clinical type of fit and the E.E.G. tracing during the fit. One baby showed both types of fits very clearly and on each

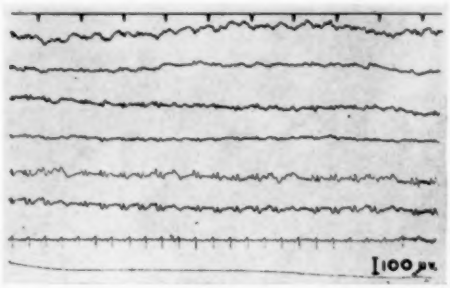


**Fig. 10A.** Case 148. These repeating sharp wave complexes occurred during the onset of a fit, during which there were repeated jerks of the eyelids occurring in time with the E.E.G. complex.

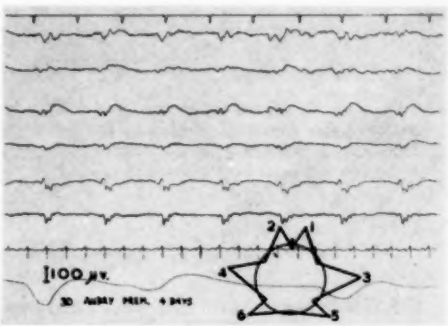


**Fig. 10B.** Wave complexes (Case 148) toward the end of fit when the jerks were becoming less frequent.

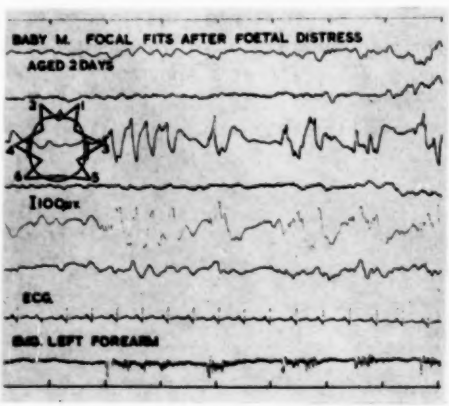


**Fig. 11.** Case 159. An example of a unilateral complex abnormality of great amplitude over the right hemisphere, occurring during a fit which consisted of focal clonic movements of the left arm. The relationship between the jerks and E.E.G. abnormality in time can be seen by the simultaneous electromyogram.

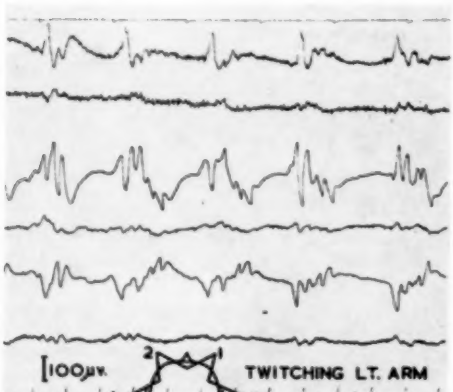


**Fig. 12.** Case 206. This was recorded during a fit when there was rhythmic jerking of the left arm. A repeating stereotyped focal complex was seen over the contralateral hemisphere.

occasion showed the appropriate E.E.G. changes.

**E.E.G. between fits.** All the abnormal features described above were seen in records obtained between fits or immediately after a single episode. In 6 infants, however, who had undoubted clinical fits with focal twitching or generalized tonic spasm, a total of 15 interseizure records made within 24 hours of the fits were apparently normal. Examination of the abnormal interseizure record shows certain correlations:

1. Small amplitude records were characteristic of premature babies having intermittent apnea with tonic or focal clonic fits.

2. Repeated focal slow wave or slow wave and sharp wave complexes were seen in cases of unifocal or multifocal clonic fits. There were several examples among the babies with focal clonic fits of E.E.G. abnormalities in the interseizure record similar to those taking place during fits. These changes might last several seconds, increasing in amplitude and decreasing in frequency and sometimes showing spread over the head. Sometimes they gradually disappeared, but sometimes they persisted until a fit took place.

3. Multiple large amplitude spikes were seen only in the case of the 2 siblings mentioned above but in these infants they were seen in many almost identical records. Repeated focal sharp waves of relatively short duration and rhythmic slow activity showed no obvious relationship to the type of fit or to the clinical condition.

## PROGNOSIS

Most of these babies who suffered from fits in the neonatal period have subsequently been re-examined and only those who have died or who are more than 1 year old (31 cases) are included in this discussion. Some

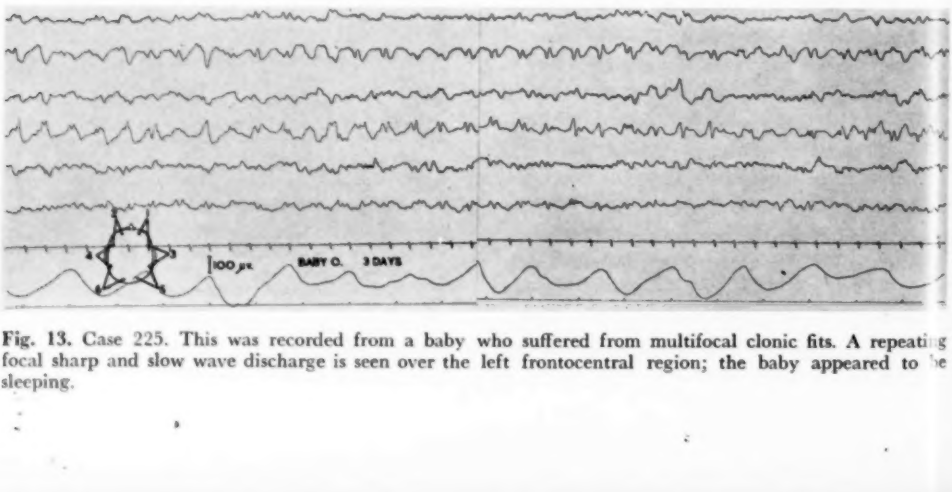


**Fig. 13.** Case 225. This was recorded from a baby who suffered from multifocal clonic fits. A repeating focal sharp and slow wave discharge is seen over the left frontocentral region; the baby appeared to be sleeping.

**Table IV**

| *Interseizure E.E.G. abnormalities other than simple flattening* | *Clinical condition at one year or more of age* | | |
|---|---|---|---|
| | *Normal* | *Abnormal* | *Dead* |
| Unilateral | 6 | 1 | – |
| Bilateral | 2 | 8 | 2 |

have clear evidence of mental or motor defect; some have continued to have fits; some are apparently normal, although it is clear that this cannot be said with finality in children so young. The neonatal records of these babies have been re-examined to look for factors of possible predictive value. With 2 exceptions none of the circumstances, clinical or electroencephalographic, of the original illness appeared to bear any definite relationship to the eventual outcome. Table IV suggests that there may be a relationship between the finding of unilateral or bilateral interseizure abnormalities (other than small amplitude) and prognosis.

Using the 2 by 2 contingency tables (Finney, 1948) the proportions of normal and abnormal live babies who had unilateral and bilateral E.E.G. abnormalities differ at the 95 per cent level of probability. Moreover, of the 8 out of 10 babies with bilateral interseizure E.E.G. abnormalities who developed abnormally, 5 show evidence of gross cerebral disorder (see Table I). The 2 who have developed normally had doubtfully abnormal E.E.G.'s.

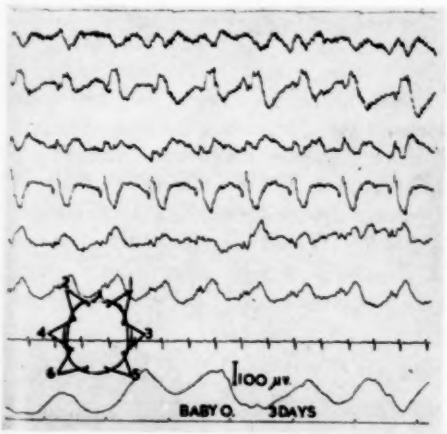


**Fig. 14.** Case 225. The same baby as in Fig. 13, but this was recorded during a generalized clonic fit which had shown Jacksonian progression at the onset. The E.E.G. shows a repeating rhythmic complex of alternating slow and sharp waves over the left hemisphere and also less clearly on the right.

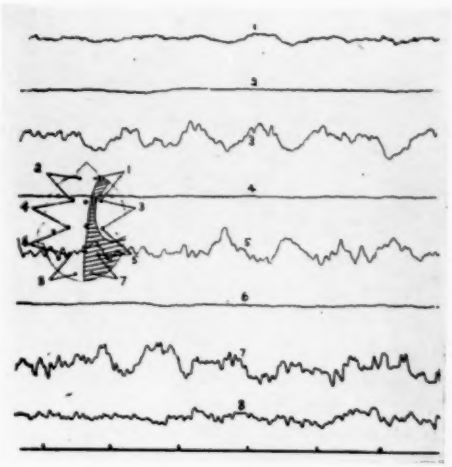

**Fig. 15.** A case of porencephaly showing a grossly asymmetrical E.E.G. The shaded area in the diagram corresponds to the shadow of cerebral tissue seen on transillumination of the head. Electrical activity is only recorded from electrodes on or near this shadow.

The 1 out of 7 babies with unilateral interseizure E.E.G. abnormalities recorded as abnormal had focal fits in association with hemorrhagic disease of the newborn and probably intracranial hemorrhage. He now appears normal in intellectual and motor function but had 1 fit in association with fever at 11 months of age.

**History.** A postmature baby, who was delivered with forceps, showed signs suggesting placental insufficiency (little subcutaneous fat; scaly dry skin) and bruising over the left parietal area. At 2 days of age bleeding took place from skin creases on the limbs, and marked pallor was noticed. The anterior fontanelle was tense, and the baby's cry was high pitched. Hemoglobin was 7.3 grams per

Fig. 16. This was the general appearance of the baby with porencephaly at 3 months.

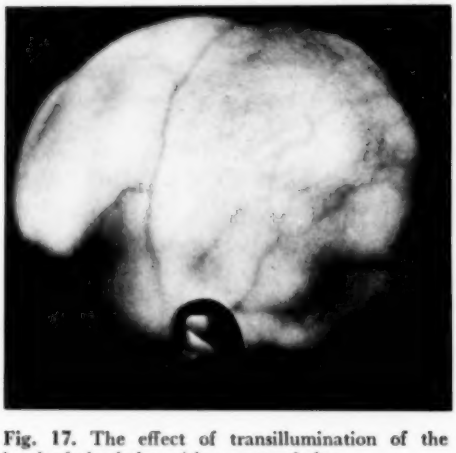

Fig. 17. The effect of transillumination of the head of the baby with porencephaly.

100 ml., platelets normal, and prothrombin activitiy 10 per cent of normal. He was treated with vitamin K and blood transfusion, with improvement in general condition. Lumbar puncture and subdural taps were not performed. At 3 days of age he had a generalized tonic fit. At 4 days left ptosis and left mydriasis were present. At 5 days there were repeated focal fits consisting of clonic movements of the right forearm, which recurred for 36 hours.

E.E.G. at this time showed focal slow sharp waves in the left parieto-occipital region (Fig. 24).

The baby subsequently appeared to be normal, but at 11 months of age had a prolonged focal clonic fit involving the right limbs a few hours after the onset of an acute febrile upper respiratory infection. Following the fit there was paralysis and hyporeflexia of the right arm and leg for 12 hours. E.E.G. (Fig. 25) showed diminished amplitude over the left cerebral hemisphere and a very occasional focal spike in the right frontal region. At 18 months he has had no further fits; he shows a definite preference for the left hand and minimally increased tendon reflexes in the right arm, but otherwise no signs of hemiparesis. Head circumference is normal. Mental development appears normal. Subsequent E.E.G.'s have been normal and showed no asymmetry.

However, the duration of the convulsive illness in the neonatal period appears to be of more practical importance in assessing prognosis than does the finding of unilateral or bilateral interseizure E.E.G. abnormalities (Table V). The significance of the duration

**Table V***

| *Duration of fits in neonatal period* | *Clinical condition at 1-year or more of age* | |
|---|---|---|
| | *Normal* | *Abnormal* |
| Less than 2 days | 9 | 1 |
| More than 2 days | 2 | 8 |

*The same test of significance was used in both Tables IV and V. The proportions here differ at the 99 per cent level of probability.

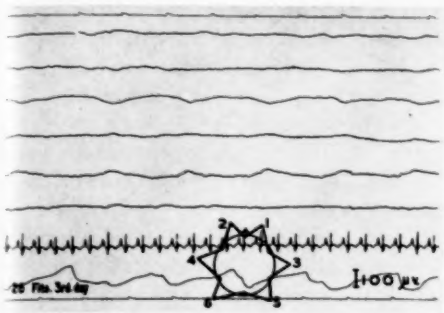


**Fig. 18.** Case 61. This E.E.G. was obtained from the same baby as in Figs. 5 and 6 and shows almost complete electrical silence at the onset of a severe symmetrical tonic spasm.

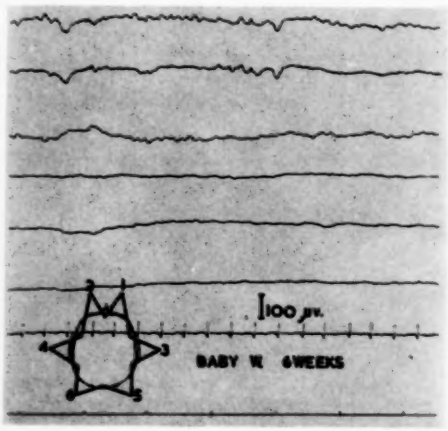


**Fig. 19.** Case 197. Another baby with porencephaly who had fits in the neonatal period. This record at 6 weeks shows generalized small amplitude.

of the illness in relation to prognosis has been emphasized by Minkowski and his colleagues.[26]

## DISCUSSION

In the light of the experience gained from this survey the questions posed in the introduction may be discussed:

1. The 6 abnormalities described above have not been seen in over 150 E.E.G.'s of normal full-term and premature infants in the first 10 days of life. It is likely that the list of abnormalities could be extended, but the largely arhythmic and variable nature of the E.E.G. in the newborn makes it difficult to distinguish minutiae of variation and the changes described as abnormal have been striking and relatively simple.

2 and 3. In this series abnormal E.E.G.'s have invariably been accompanied by abnormal clinical states. This is necessarily so since, in the absence of previous standards, clearly defined assessment of abnormality in individual records must depend less on their intrinsic characteristics than on the clinical associations. However, the reverse proposition does not hold. Interseizure E.E.G.'s in babies having undoubted fits may be normal (as in 6 out of the 41 cases here reported) and a clinical state suggestive of cerebral disorder but without fits, for instance following traumatic delivery, has not always been accompanied by abnormal E.E.G. findings. Although E.E.G. abnormalities were always found during fits, the only abnormality might be a flattening of the tracing, and, if the amplitude were already small, for instance, following traumatic delivery or in anoxic premature babies, no change might be seen at the onset of, and during, a fit.

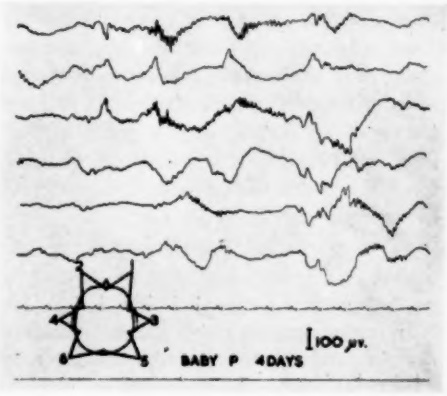


**Fig. 20.** Case 168. This was a premature baby who suffered from fits and there was associated hypoglycemia. The record shows generalized excessive rhythmic activity at 14 to 20 cycles per second.

These facts clearly limit the usefulness of the E.E.G. in determining whether or not episodic disturbances or abnormal movements in the newborn infant really are convulsive.

4. The treatment of neonatal convulsions must consist either of relieving the underlying condition such as anoxia, hypoglycemia, hypocalcemia, intracranial hemorrhage, and the like, or of symptomatic drug treatment. Unilateral flattening of the E.E.G. has been reported in neonatal subdural hematoma. Accurate correlation with anoxia and other biochemical changes has yet to be determined, but it seems doubtful if the E.E.G. will provide diagnostic evidence of biochemical disturbance, which cannot be more easily elicited in some other way. The E.E.G. may prove to be of diagnostic importance in the detection of persistent focal abnormalities.

The E.E.G. in the newborn may have some bearing on ultimate prognosis in terms of motor and mental defect, although, again, clinical correlations appear to be of greater significance. Possibly its greatest interest will lie in the relation of focal cerebral seizures in childhood to birth injury and anoxia.

If the practical importance of the E.E.G. in the newborn infant at present appears slight, however, its theoretical implications are of the greatest interest. Ribstein and Walter[29] state that the E.E.G. in the neonatal period shows that neonatal fits appear to be of focal cerebral origin and that the spread of abnormal discharges is characteristically not accompanied by bilateral synchrony. The present survey confirms these findings. The clinical association in cases of focal fits, characterized both by focal clonic movements and by focal E.E.G. abnormalities, suggests that focal hemisphere brain damage is in many cases the consequence of previous anoxia.

In contrast, the other major group of fits observed are those accompanying acute anoxia, characterized clinically by symmetrical tonic spasm, sometimes preceded or followed by a few clonic jerks, and electroencephalographically by flattening of the record. This is in keeping with the clinical and E.E.G. findings in acute anoxia summarized by Gastaut and his colleagues,[21] which are ascribed to depression of the forebrain and the consequent release from control of caudal reticular brain stem activity. The bilaterally symmetrical synchronous slow waves seen in some phases of both types of fits, might be interpreted as being of brain stem origin, either induced by biochemical deviations or secondary to focal cerebral disturbance.

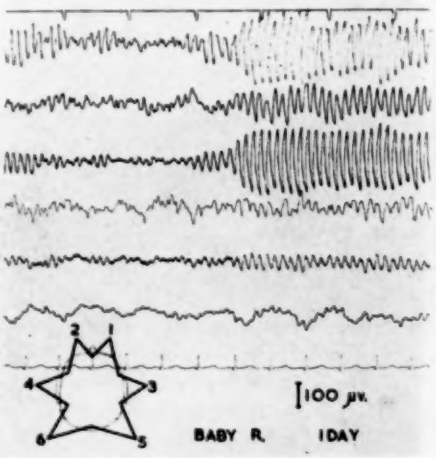


**Fig. 21.** Case 127. This record from a baby with severe cerebral malformation shows bursts of clearly defined rhythmic high potential 8 cycles per second activity with phase reversal in the right frontal region.

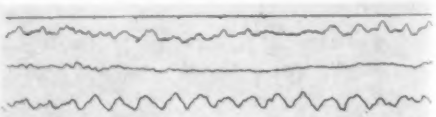


**Fig. 22.** An artefact in the E.E.G. due to head movements associated with respiration.

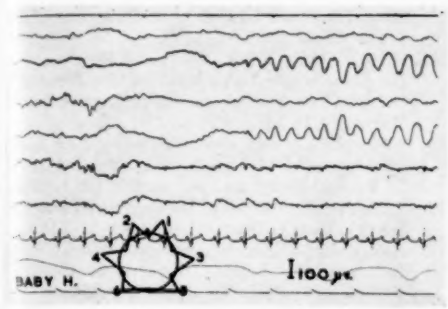


Fig. 23. Focal rhythmic activity associated with sucking movements.

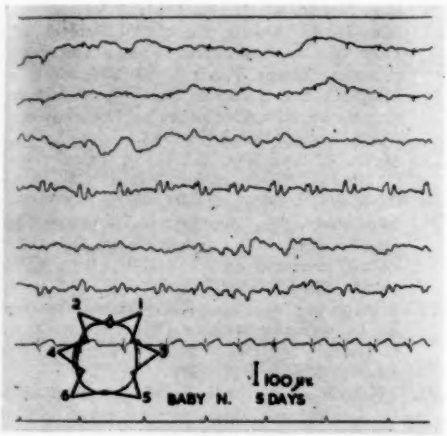


Fig. 24. Case 216. Repeating left-sided focal sharp waves occurring during a focal fit consisting of clonic movements of the right forearm.

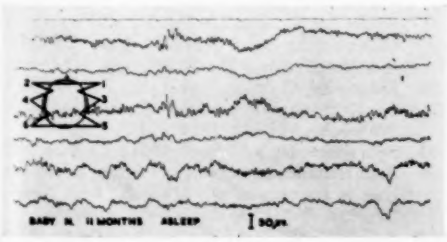


Fig. 25. Case 216. Record obtained from the same baby as in Fig. 24, 5 days after a prolonged right sided clonic fit, when 11 months old. Sleep was induced with Seconal Sodium. There are diminished amplitude of the activity over the left hemisphere and a focal spike in the right frontal region.

## CONCLUSIONS

Any investigation involving a steady physiologic state in the newborn is difficult to carry out, as is any investigation in a sick newborn baby, but obtaining an electroencephalogram presents no special difficulties. Fits in the newborn infant are usually accompanied by striking E.E.G. abnormalities, and although the practical value of the E.E.G. at present seems slight, it is felt that an E.E.G. should be as much a part of the investigation of fits in the newborn infant as it is in older children and adults.

## SUMMARY

1. An account is given of the E.E.G. abnormalities encountered in 41 infants who developed convulsions in the early neonatal period.

2. Certain relationships were noted between the type of fit and the E.E.G. abnormality.

3. The main types of fit seen in the newborn baby, distinguished both clinically and electroencephalographically, are twofold: the first type is possibly the consequence of previous anoxia and the second is associated with acute anoxia.

4. The significance of the neonatal E.E.G. in terms of disordered physiology, diagnosis, and prognosis are discussed.

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# A syndrome of phenylketonuria with normal intelligence and behavior disturbances

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THE diagnosis of phenylketonuria usually depends upon the association of mental retardation with one or more characteristics of a symptom complex that includes light hair, fair skin, blue eyes, eczema, seizures, and abnormal electroencephalograms. Impaired mental ability was thought to be manifest in the recognition of these patients. In 1939 Jervis[1] reviewed 200 cases of phenylketonuria and concluded that there was "pronounced mental defect in all cases." Two patients in his series had an I.Q. as high as 60, both of whom were described as high-grade, well-behaved defectives. Others have agreed with this observation, although most of the reported patients have come from mental institutions. The discerning physician suspected phenylketonuria if his patient was mentally deficient and showed some or all of the above characteristics.

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However, phenylketonuria does not invariably lead to impaired mental ability. In 1949 Cohen and Kozinn[2] described the father of a mentally deficient phenylketonuric child who had the same disease. He worked steadily as a presser of gloves and was generally asymptomatic: he had an I.Q. of 69. Cowie[3] reported 2 cases of phenylketonuria with borderline intelligence. Low, Armstrong, and Carlisle[4] reported a case in a child 2½ years old who had an I.Q. of 82. Only the odor of phenylacetic acid led to detection of the disease, for she was otherwise normal. They also described a 50-year-old man with an I.Q. of 67 who was institutionalized for "social reasons." He had fair, sensitive skin, was "emotional" and worried about minor things which would not ordinarily bother an adult. He completed grammar school and held a job at the institution. Leonard and McQuire[5] recently reported the case of an 8-year-old girl with an I.Q. of 80. She feared heights and dogs, dressed backward, and had difficulty pronouncing consonants, but showed none of the characteristics usually associated with phenylketonuria. Bickel and Gruter[6] observed a child who had biochemical findings characteristic of phenylketonuria, an I.Q. of 70, and evidence of psychic disturbances. In Table I

are summarized reports of 10 patients with biochemical characteristics of phenylketonuria, but without severe mental defect.

It is the purpose of this paper to report 2 cases of phenylketonuria in which a similar psychological and psychomotor behavior pattern led to the diagnosis in spite of normal or near-normal mental capacity. The diagnosis was made by one of us (H.C.S.) whose previous observation of phenylketonuric patients led to a feeling that these 2 children "looked and acted" as if they had phenylketonuria. The impression was confirmed in each case by a positive ferric chloride test. Since phenylketonuria is usually suspected because a child is mentally retarded, it is important to realize that the illness manifests itself in other recognizable ways apart from mental retardation and the signs previously mentioned. This fact may permit the discovery of the disorder and of the gene in families that do not have mentally retarded members. The recognition of the abnormal trait may help to discover the carrier state in other members of such families and prevention of the disease can be aided by appropriate advice.

## CASE REPORTS

**Case 1.** D. R., a $3\frac{7}{12}$-year-old male, was admitted to the hospital for a number of complaints including irritability, extreme hyperactivity, outbursts of temper, unmanageability, poor eating habits, inability to be toilet trained, nocturnal wakefulness, and retarded speech development. He was considered difficult as an infant, and these complaints became more pronounced as he grew older.

He was the product of a full-term, normal pregnancy and delivery. Two younger siblings are in good health. Developmental milestones were accomplished within the proper limits of time except for speech. Pronunciation was poor and sentence formation did not occur until he was more than 3 years old. His mother felt that his coordination in accomplishing small manual tasks was poor; he had been observed to stumble frequently. Much apprehension occurred when new situations arose. Passing buses, cars, and trucks caused much excitement, often accompanied by rapid hand and finger movements, stretching upward on his toes or rocking back and forth.

On examination, D. R. was a well developed but thin child whose measurements placed him above the tenth percentile for weight and below the twenty-fifth percentile for height. He was described as having a "hazy, faraway look" and was extremely apprehensive, but when reassured he answered all questions with interest, giving correct answers. His speech was very difficult to understand. His hair was light brown, eyes were dark, and the skin was not unusually fair. The physical examination, including neurological examination, was essentially negative. The characteristic odor of phenylacetic acid was noted about the clothing and bed. Hemograms and roentgenograms of the skull and long bones were within normal limits for his age. Psychological examination revealed a mental age of 3 years, 4 months, and an I.Q. of 93. D. R. showed interest in the tests and was responsive, but his manipulation of test objects was awkward. The serum phenylalanine levels determined by the chromatographic method[9] were 13 mg. and 15 mg. per 100 ml., respectively, on successive days. The normal range is 1-4 mg. per 100 ml. D. R. was placed on a diet of low phenylalanine content as described by Berry, Sutherland, Guest, and Umbarger,[10] using Lofenalac as the protein substitute. After the diet had been continued for one year he showed remarkable changes. He now speaks plainly, shows good coordination, and has lost all the apprehension previously described. He plays well with other children and no longer demonstrates the hyperactivity or extreme irritability which made him an unmanageable child. He now continues to do well on the diet.

**Case 2.** K. H. was first seen at the Children's Hospital in 1958 when she was 7 years old. At that time she had severe eczema complicated by infection. The eczema had appeared first at the age of 4 months and

Table I

| Reference | Age | I.Q. | Serum phenylalanine | Other characteristics |
|---|---|---|---|---|
| Cohen and Kozinn[2] | | 69 | | Worked as presser of gloves; no symptoms of phenylketonuria |
| Cowie[3] | 7 years | 76 | | |
| Armstrong and Tyler[7] | 13 months | 78 | | Deteriorated by age 2 |
| Low, Armstrong, and Carlisle[4] | 2½ years | 82 | 25-31 mg./100 ml. | Normal physical and mental development<br>Odor of phenylacetic acid |
| | 50 years | 67 | 22 mg./100 ml. | Institutionalized for social reasons; emotional, worried about minor things |
| Leonard and McQuire[5] | 8 years | 80 | 36.5 | Feared heights, dogs; dressed backward; difficulty in pronouncing consonants |
| Bickel and Gruter[6] | 5 years | 70 | 7-12 mg./100 ml. | Psychic disturbance |
| Caudle[8] | 3½ years | 120 | 13 mg./100 ml. | Normal development<br>No unusual fears; random rocking motions at times |
| Sutherland et al. (this report) | 4 years | 93 | 13-15 mg./100 ml. | See text |
| Sutherland et al. (this report) | 7 years | 67 | 25 mg./100 ml. | See text |
| Coates, Norman, and Woolf[13] | 9 years | 103 | 5 mg./100 ml. (fasting) | Gower's muscular dystrophy |

persisted with severe manifestations until she was 4½ years of age. It then became less troublesome, but asthmatic attacks followed. The current exacerbation of skin eruption occurred soon after an attack of the measles.

K. H. was born after an induced labor following a normal, full-term pregnancy. Two older and 2 younger siblings are well. Her mother felt that her early development, such as reaching for objects and rolling over, occurred at a time comparable with that of her siblings. She sat up at 5 to 6 months of age, but with the onset of the severe skin eruption she "sat and did nothing." She did not crawl and failed to walk until 3 years of age. Toilet training did not occur until age 4, and speech was not accomplished until she was 5 years old. Initially she did not talk plainly and failed to pronounce consonants well. There was no definite history of seizures, although for a brief period at age 1½ she was noted to "stiffen her arms" for several seconds.

K. H. had always been regarded as a "fearful" child. New situations or persons were met with apprehension. The sight of an ironing board being taken from a cupboard caused concern. At times she seemed very stubborn and negativistic. Her mother said she seldom sat or stood quietly, and she often rocked back and forth.

On examination, K. H. was a thin child who held herself stiffly, with slightly hunched shoulders. Measurements placed her below the third percentile for weight and near the tenth percentile for height. She had little facial expression, appearing dull and listless, and regarded one with fearful, watchful eyes. She had a peculiar pallor, although anemia was not present. The skin was roughened by a scaling eczematoid eruption.

She answered all questions readily but with slow, hesitant speech. Pronunciation was adequate. She walked with a stiff-legged gait and carried her right arm at a wide angle. Her hair was light brown in color and her eyes were dark. Neurological examination was negative. Hemograms and roentgenograms of the skull were normal. Psychological testing by the Stanford-Binet Scale indicated an I.Q. of 65. The Goodenough Drawing Test rated her at 72. Since K. H. attended school and had been promoted from the first grade, the higher rating might be a more accurate assessment of her intellectual capacity. Serum phenylalanine concentration was 25 mg. per 100 ml.

K. H. was placed on a low phenylalanine diet which she accepted well while hospitalized. There was general agreement that she became livelier, more friendly and cooperative. She was discharged on this regimen, but the diet was discontinued several days later because of the onset of severe asthma and the sympathetic upheaval it caused among the other siblings.

## DISCUSSION

The 2 patients described in this paper, one with mental ability within the normal range and one only slightly below normal, seem to have a similar psychomotor and psychological behavior pattern.

This may be summarized as follows:

| | |
|---|---|
| 1. Dull expressionless faces: | A "faraway, hazy look." |
| 2. Negativistic behavior: | Refusal to perform tasks, unfriendliness, stubbornness |
| 3. Apprehensive behavior: | Fear of simple objects, persons, new situations, new places. |
| 4. Emotional outbursts: | Quarrelsomeness, temper tantrums, easily upset over minor incidents. |
| 5. Speech disturbance: | Delayed onset of speech, difficulty in pronouncing consonants, speech difficult to understand. |

The cases reported by Low, Armstrong, and Carlisle[4] and Leonard and McQuire[5] in which there was little or no impairment of mental ability suggest oddities of behavior which might well correspond to the behavior pattern we are reviewing. They, together with our patients D. R. and K. H., suggest that attention should be given to this heretofore unrecognized symptom complex which may enable a physician to diagnose phenylketonuria in patients who appear to be of normal intelligence.

It is pertinent to point out why the recognition of the older phenylketonuric child, mentally unimpaired, is important. We now know that mental retardation can be prevented by the early diagnosis and treatment of phenylketonuria in the very young infant. Therefore, we should identify the families in which the abnormal gene is present, and thus the families into which a phenylketonuric child might be born. The recognition of a typical mentally retarded phenylketonuric child in a family can accomplish the purpose; but equally significant is the discovery of a family in which there is an afflicted child of normal mental capacity. Perhaps the behavior pattern we have reviewed will aid in the discovery of such families.

Although it has been reported that older phenylketonuric patients do not benefit from a phenylalanine-restricted diet, as evidenced by the lack of improvement in mental capacity, it has been observed that several older, severely afflicted mentally retarded patients who demonstrated severe psychomotor agitation became more calm and manageable.[10] To these findings may be added our observation of D. R. whose behavior improved while receiving diet treatment. This should lead to a revision of the concept that a phenylalanine-restricted diet is of no value in the treatment of the older child. In fact, a treatment which allows an otherwise mentally competent child to function normally would seem to be invaluable.

The serum phenylalanine concentration in both D. R. and K. H. were considerably lower than those found in children with

marked retardation. This finding seems to contradict the opinion of Borek and coworkers[11] who found no correlation between serum phenylalanine levels and mental performance expressed by I.Q. The range of intelligence quotients in their patients was from 5 to 47. The range observed in serum phenylalanine concentration was 19 to 47 mg. per 100 ml. Armstrong and his associates[12] noted a direct relationship between ortho-hydroxyphenylacetic acid excretion and blood levels of phenylalanine in a series of 12 phenylketonuric patients. They concluded, on the basis of Borek's statement, that neither excretion of ortho-hydroxphenylacetic acid, nor serum phenylalanine concentration was related to the degree of mental defect. However, the patient in the group with the highest I.Q., 70, had the lowest serum phenylalanine concentration, 22 mg. per 100 ml. The data in Table I indicate that lower values for serum phenylalanine concentration are often found among phenylketonuric individuals who have normal or nearly normal intelligence.

## SUMMARY

1. Two patients with biochemical characteristics of phenylketonuria have been described, one with normal and the other with nearly normal mental ability.

2. On preliminary examination a previously unreviewed psychological and psychomotor symptom complex common to both patients was recognized, which made diagnosis possible despite normal mental capacity.

3. A phenylalanine-restricted diet employed in treatment of one patient brought about alleviation of psychomotor and psychological agitation, suggesting that dietary therapy in the older phenylketonuric child may be beneficial.

4. There appears to be a definite relationship between I.Q. and serum phenylalanine concentration in these 2 children with normal and nearly normal intelligence.

5. The diagnosis of phenylketonuria in a child with normal mental ability may lead to recognition of families in which the abnormal gene might not otherwise have been discovered.

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# *Leucine-induced hypoglycemia*

## *I. Clinical observations and diagnostic considerations*

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THE syndrome of idiopathic hypoglycemia has long been suspected to represent a heterogenous group of unrelated etiological entities, but not until the report of Cochrane, Payne, Simpkiss, and Woolf[1] in 1956 were some instances of otherwise idiopathic hypoglycemia identified as a specific entity. They demonstrated that hypoglycemic reactions in some patients were precipitated by the ingestion of proteins. The administration of casein resulted in hypoglycemia in these patients, whereas the administration of gelatin produced little effect on the blood sugar levels. Since both tyrosine and leucine are present in casein in greater amounts than in gelatin, these two amino acids were administered individually to the affected children. Tyrosine was without effect, but leucine resulted in a fall in the blood sugar level comparable to that caused by casein. Thus, some patients with "idiopathic hypoglycemia" have a clearly defined entity, leucine-sensitive hypoglycemia. Recent reports[2-7] indicate that this disorder may comprise a significant portion of the so-called idiopathic hypoglycemia in infants. Only two of these studies have been presented in detail.[1, 7] The present study is a report of our clinical experiences with 2 patients with leucine-induced hypoglycemia.[8, 9]

### METHOD OF STUDY

The blood glucose response was measured during the following procedures: (1) oral glucose tolerance test with 1.75 Gm. per kilogram of glucose; (2) glucagon* tolerance test; (3) oral L-leucine test with 150 mg. per kilogram of aqueous L-leucine; and (4) intravenous L-leucine test with 75 mg. per kilogram. The L-leucine for intravenous administration was prepared as follows: Chromatographically pure L-leucine† was dis-

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solved in a pyrogen-free 0.45 Gm. per cent aqueous solution of sodium chloride at a concentration of 20 mg. per milliliter. The preparation was autoclaved in rubber-toppered bottles at 250° F. at 15 to 18 pounds gauge pressure for 10 minutes. The leucine was unaltered as demonstrated by paper chromatography. No untoward effects were detected when the preparation was administered intraperitoneally to rats at 10 to 20 times the per kilogram dose given the patients. The L-leucine was injected rapidly within a period of one minute. Blood sugar levels were determined by the Nelson-Somogyi method[10] with the use of capillary blood, unless otherwise specified. All test procedures were performed after fasting periods of 2 hours.

Urine was examined for excess amino acids by measuring the total alpha-amino nitrogen in a 24-hour urine collection, by a modification of the Troll-Cannan method.[11] Results are expressed as milligrams of alpha-amino nitrogen relative to a leucine standard. Random urine samples were examined for amino acid and sugars by paper chromatography. The methods described by Smith[12] were used. For amino acids, the first solvent system consisted of a fresh mixture of 24 parts *n*-butanol, 6 parts glacial acetic acid, and 10 parts water. After the paper was dried and rotated 90 degrees, it was placed in the second solvent system consisting of 200 parts phenol and one part ammonium hydroxide. For sugars, the solvent system consisted of 12 parts ethyl acetate, 5 parts pyridine, and 4 parts water.

## CASE REPORTS

**Case 1.** J. C. (St.C.H.C. No. 550045), a white male born May 13, 1958, was first seen in our clinic at the age of 4 weeks. The mother, a 24-year-old white woman, gravida v, para iii, who had had 2 abortions, is now in good health, as are the 27-year-old father and 2 older male siblings. The parents' marriage is nonconsanguineous, and a detailed search into four generations of both the maternal and paternal sides of the family failed to reveal anyone with apparent hypoglycemia. There is a history of diabetes with onset at maturity in the paternal grandfather.

The patient was born at term, weighing 9 pounds, 8 ounces. At the time of delivery the mother was in a state of pre-eclampsia. After a difficult spontaneous delivery, the infant was apneic and had cardiac arrest. He was revived by resuscitative measures which included the intracardiac administration of epinephrine. Immediately following delivery the mother developed severe eclampsia, but recovered sufficiently to be discharged on the fifth postpartum day.

After the initial resuscitative measures, the infant was transferred to an incubator. He had constant "twitching" of the extremities, general hyperirritability, poor muscle tone, and the Moro reflex was absent; his cry was lusty and suggestive of pain. During the first 24 hours, two additional 2-minute periods of apnea were noted. Cerebrospinal fluid examined at birth was within normal limits.

The patient's course appeared similar to that of an infant of a diabetic mother. Therefore, he was given frequent glucose-water feedings by gavage.[13] On this regimen he seemed to improve, and on the third day he was removed from the incubator and given "frequent" Similac feedings by bottle.

The infant was sent home on the tenth day of life, weighing 8 pounds, 11 ounces, and Similac feedings were continued at 3 to 4 hour intervals. Because of persistent and marked irritability, limpness, and 30 to 40 "twitching episodes" daily, he was admitted to St. Christopher's Hospital for Children for further evaluation.

At the age of 4 weeks, the time of our first examination, he weighed 10 pounds, 4 ounces, and manifested irritability and "trembling and jitteriness." His head measured 14¾ inches in circumference, and the anterior fontanel was small. Deep tendon reflexes were hyperactive. Head lag was marked, and he was excessively flaccid. A social smile and Moro reflex were present. Bilateral subdural punctures yielded no fluid. Hemogram, urinalysis, and serum cal-

cium (11.0 mg. per cent) and phosphorus (6.0 mg. per cent) levels were within normal limits; a 2-hour postprandial blood sugar determination was 34 mg. per cent.

Additional blood sugar levels were measured and confirmed the presence of severe, persistent hypoglycemia. The formula was changed to frequent feedings (every 1 to 2 hours) of Nutramigen, and therapy with prednisone (10 to 20 mg. per day) was instituted at the age of 6 weeks. After 2 weeks prednisone was discontinued, and corticotropin (10 to 20 units per day) was substituted. On this regimen numerous twitching episodes, overt seizures, and periods of "wilting" continued to occur in association with low blood sugar levels (24 to 50 mg. per cent). When the feeding interval was prolonged more than 4 hours, he would become hypotonic and apathetic toward feeding. Seizures were observed to occur at random intervals which bore no relationship to the feeding schedule. Hypoglycemia was demonstrated in association with some of these seizures.

Therapy with corticotropin was continued for 9 months. During this time, the feeding intervals were lengthened gradually to 4 hours. Even though the infant improved, he continued to feed poorly. Minor illnesses provoked "wilting" episodes, during which he became hypotonic and refused bottle feedings. One or 2 ounces of glucose water 15 to 60 minutes after each feeding proved helpful during these episodes.

It was possible by continually maintaining the infant on corticotropin to decrease the number of hypoglycemic spells, but he subsequently developed marked Cushingoid characteristics, (Fig. 1) manifested by obesity, acne, hirsutism, hypertension, and osteoporosis. Because of these manifestations, the dose of corticotropin was progressively reduced and discontinued without apparently affecting the infant's hypoglycemic course. As he grew older he appeared to tolerate hypoglycemia with fewer symptoms. Throughout the entire period of steroid therapy there was failure of developmental progress. Developmental testing at the age of 19 months, according to the standards of Gesell, placed him at a 6 to 8 months' level of achievement.

**Fig. 1A.** Patient 1 (J. C.) at 9 months of age after he had been on corticotropin therapy for 7 months. Note the severe Cushingoid manifestations.

At 19 months of age, he was a small (17 pounds, 3 ounces), sociable infant who measured 27 inches in length and had a head circumference of only 16¾ inches. Since this time his diet has consisted of Similac, puréed vegetables and fruit, and specifically excludes foods high in protein.

**Case 2.** R. L. (St.C.H.C. No. 593790), a Negro female born April 16, 1957, was referred to St. Christopher's Hospital for Children for further study and management of hypoglycemia at 29 months of age. The mother was a 26-year-old gravida v, para v, unwed Negro; the presumed father was a 44-year-old Negro. The parents' union

was nonconsanguineous, and neither parent could recall any similar disorders or diabetes in their families. The mother denies symptoms of toxemia of pregnancy during this or previous pregnancies but was hospitalized with severe pre-eclampsia during a subsequent pregnancy.

The infant, the product of a 9 months' gestation, weighed 6 pounds, 11 ounces at birth, and was apparently normal. She was started on a cow's milk formula while in the nursery, and her growth and development appeared normal during the first several months. At 4 months of age she had a seizure characterized by "stiffening all over, frothing at the mouth, staring eyes, and gross tremors," and failure to respond to her mother's voice. This episode occurred approximately 3 hours after an early morning feeding. During the same day she had two additional similar episodes. She was seen in the Pediatric Clinic of the Delaware Hospital, Wilmington, Delaware, on the following day. At that time she was in no apparent distress. The only abnormal finding was that of a relatively small circumference of her head (14¾ inches) when compared with her weight (12 pounds, 9 ounces) and length (22½ inches). The following morning a fasting blood sugar level was 46 mg. per cent (Folin-Wu). The serum calcium level (11.0 mg. per cent) and phosphorus level (5.0 mg. per cent) were within normal limits. Repeated blood sugar determinations confirmed the presence of severe, persistent hypoglycemia (18 to 50 mg. per cent—Folin-Wu).

**Fig. 1*B*.** Patient 1 (J. C.) at 17 months of age after corticotropin therapy had been discontinued for 6 months.

Corticotropin therapy (8 to 20 units daily) was instituted. The infant showed a good response in that she had only an occasional seizure. Random blood sugar levels, although not normal, were generally 10 to 30 mg. per cent higher than the pretreatment levels. This therapy was continued until the age of 2 years during which time she became markedly Cushingoid.

At 2 years of age it was demonstrated that she was sensitive to leucine. At this time the 1 quart of cow's milk daily in the diet was reduced to 2 glasses daily. She continued to have occasional hypoglycemic episodes and seizures and was transferred to St. Christopher's Hospital for Children.

On physical examination at 29 months of age she weighed 27 pounds, measured 35½ inches in length, and had a head circumference of 17½ inches. The Cushingoid condition had abated, and she seldom had an overt hypoglycemic episode, although she frequently had hypoglycemia (19 to 50 mg. per cent). Developmental testing at the age of 29 months, by the standards of Gesell, revealed an attainment of 21 months.

## RESULTS

**Glucose tolerance tests.** During the first oral glucose tolerance test on Patient 1 (J. C.) tremors and bradycardia occurred 75 minutes after the glucose feeding. Because of these symptoms the test was interrupted by the administration of epinephrine after 100 minutes. The blood sugar values were: fasting, 52; at ½ hour, 96; at 1 hour, 103; and at 1½ hours, 76 mg. per cent, respectively. Forty minutes after administration of epinephrine the blood sugar level was 116 mg. per cent. Three days later when the baby was 5 weeks of age the test was repeated and is one of those presented in Fig. 2. Continuous electroencephalographic tracings during this test revealed abnormal changes during hypoglycemic periods. One and one-half hours after the administration of the glucose, twitching of the arms and head and sinus arrhythmia developed. One half hour later generalized jerking movements occurred which persisted for 15 minutes. The infant was asleep and snoring at the completion of the test at 4 hours. In Fig. 2 are also shown the results of two additional glucose tolerance tests performed while the patient was being treated with prednisone. During the second of these tests (after treatment for 5 weeks) the patient developed tachycardia (200 per minute), irritability, sweating, and pallor after 2 hours. At 2 hours and 45 minutes the test was terminated by the administration of epinephrine. It is noteworthy that there was remarkably little difference between the results of the glucose tolerance tests before and during treatment with prednisone.

The initial glucose tolerance test on Patient 2 (R. L.) was performed in the Delaware Hospital, Wilmington, Delaware, when the baby was 4 months of age. The results of this test were as follows (Folin-Wu): fasting, 46; at ½ hour, 91; at 1 hour, 133; at 2 hours, 145; at 3 hours, 87; at 4 hours, 38; at 5 hours, 18; and at 6 hours, 20 mg. per cent, respectively.

Oral glucose tolerance tests were repeated

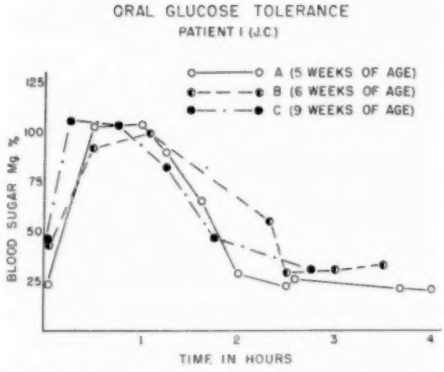


**Fig. 2.** *A*, Glucose tolerance test obtained on June 17, 1958, before prednisone therapy was instituted. *B*, Glucose tolerance test on June 24, 1958; the patient had received prednisone, 2.5 mg. every 6 hours since June 18. *C*, Glucose tolerance test on June 7, 1958; the patient had received prednisone as follows: from June 24 to June 30, 5 mg. every 6 hours; from June 30 to July 11, 3 mg. every 4 hours; from July 11, 1958, to day of test, 4 mg. every 6 hours.

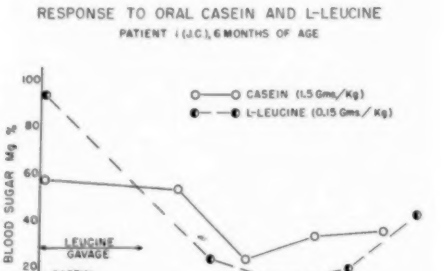


**Fig. 3.**

when Patient 1 (J. C.) was 21 months of age and when Patient 2 (R. L.) was 3 months of age. Both patients had fasting blood sugar levels (64 and 56 mg. per cent) which were higher than the values obtained in the initial tests. The curves were somewhat flatter; at 1 hour the values were, respectively, 80 and 96 mg. per cent, at 2 hours the values were 72 and 70 mg. per cent, and only after 3 to 4 hours were hy-

poglycemic values obtained (44 and 37 mg. per cent).

**Responses to epinephrine and glucagon.** *Patient 1 (J. C.).* No epinephrine tolerance test was performed; as previously pointed out, however, two of the glucose tolerance tests were terminated by the use of epinephrine and feeding because of manifestations suggestive of hypoglycemia. In each instance there was an adequate glycemic response following the administration of 0.06 ml. of 1:1,000 epinephrine subcutaneously and feeding. On the first occasion the blood sugar rose from 76 to 116 mg. per cent in 50 minutes; on the second occasion the blood sugar rose from 31 to 127 mg. per cent in 30 minutes.

Glucagon was administered on two occasions while the patient was receiving 20 units of corticotropin daily. The blood glucose levels after a 20 mcg. per kilogram dose were as follows: fasting, 75; at 50 minutes, 108; at 80 minutes, 43; and at 140 minutes, 53 mg. per cent, respectively. A 60 mcg. per kilogram dose of glucagon was administered for the second test. The blood glucose levels were as follows: fasting, 56; at 40 minutes, 88; at 70 minutes, 19; and at 130 minutes, 20 mg. per cent, respectively. The glycemic effect with glucagon was adequate. It may be noted that 30 minutes following the peak blood sugar level there was a precipitous drop to below the fasting levels.

*Patient 2 (R. L.).* The blood glucose levels during an epinephrine tolerance test were: fasting, 66; at 15 minutes, 72; at 30 minutes, 98; and at 45 minutes, 100 mg. per cent, respectively (Folin-Wu).

**Responses to casein and L-leucine.** Patient 1 (J. C.) was first demonstrated to be leucine sensitive at 6 months of age. The oral administration of both casein (1.5 Gm. per kilogram) and of L-leucine (0.15 Gm. per kilogram) on separate days resulted in a definite reduction of blood sugar levels (Fig. 3). Patient 2 (R. L.) was first tested with leucine at the age of 2 years in the referring hospital. The presumptive diagnosis of leucine-sensitive hypoglycemia was made, and she was transferred to St. Christopher's Hospital for Children at 29 months of age for further study.

Owing to the variability of blood sugar levels in patients with hypoglycemia, it was deemed desirable to determine the usual blood glucose levels in these patients during the hour of the day selected as the test period, viz., a second to third postprandial hour. These results for the 2 affected patients and for a group of control patients are shown in Table I and Fig. 4.

Following these initial observations an intravenous L-leucine test was devised to minimize variables associated with oral administration of test compounds. The two affected children were tested repeatedly by this method at various ages (Table II and Fig. 5). The blood sugar levels consistently fell more than 50 per cent from the initial level within 20 to 40 minutes and usually returned to the baseline level at 60 minutes.

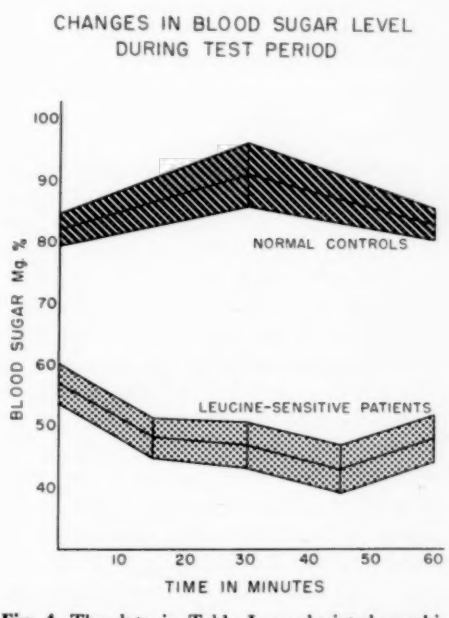


**Fig. 4.** The data in Table I are depicted graphically. The mean and plus and minus one standard error of the mean are included within the shaded areas. The test period was from the second to the third postprandial hour. No procedure was carried out other than the collection of blood specimens.

**Table I.** Changes in blood sugar levels during the test period from the second to the third postprandial hour

| | | *Blood sugar level in mg. % (time in minutes)* | | | | |
|---|---|---|---|---|---|---|
| | *Age in months* | *0* | *15* | *30* | *45* | *60* |
| *Leucine-sensitive patients.* | | | | | | |
| J. C. | 7 (on ACTH) | 54 | | | | 43 |
| | 17 | 74 | | | | 65 |
| | 17 | 70 | | | | 66 |
| | 17 | 42 | 48 | 49 | 47 | 53 |
| | 17 | 61 | | | | 63 |
| | 19 | 63 | 54 | 59 | 51 | 49 |
| R. L. | 29 | 47 | 38 | 41 | 42 | 44 |
| | 29 | 45 | | | | 25 |
| | 29 | 67 | | | | 41 |
| | 31 | 60 | 56 | 48 | 48 | 48 |
| | 31 | 49 | 46 | 37 | 29 | 33 |
| Mean | | 57 | 48 | 47 | 43 | 48 |
| S.E.M. | | 3.2 | 3.2 | 3.8 | 3.9 | 3.9 |
| *Control patients.* | | | | | | |
| E. L. | 19 | 79 | | 111 | | 91 |
| L. S. | 25 | 70 | | | | 88 |
| L. S. | 25 | 87 | | 84 | | 71 |
| E. P. | 28 | 91 | | 83 | | 81 |
| A. R. | 28 | 87 | | 94 | | 86 |
| P. McA. | 32 | 79 | | 97 | | 86 |
| W. S. | 56 | 82 | | 76 | | 76 |
| Mean | | 82 | | 91 | | 83 |
| S.E.M. | | 2.6 | | 5.1 | | 2.7 |

Concomitant with the fall in blood sugar levels the infants became progressively more irritable and this sign abated during the second half-hour of the test period. As the patients grew older the test procedure resulted in no overt symptoms other than lethargy, although the hypoglycemic effect was still demonstrable. It would appear that the 2-hour postprandial blood sugar level of Patient 1 (J. C.) has gradually increased as the child became older (Table II). The results of the leucine test performed at 20 months of age is shown in Table II, but these data have not been included in the calculation of the means because the fasting blood sugar level was more than three standard deviations removed from the mean of the remainder of the group. Three values obtained on different days at 21 months of age were 64, 69, and 70 mg. per cent, respectively.

Seven other children with hypoglycemia of undetermined etiology were tested in the same manner. Etiologically, these patients probably represent a heterogenous group. One patient (J. D.) showed hypoglycemia as early as 2 hours postprandially. The majority of the other patients exhibited hypoglycemia only after more prolonged fasting. Leucine had no effect on the blood sugar level of these children. Nine patients with no known disorder of carbohydrate metabolism served as normal controls. Intravenous leucine (75 mg. per kilogram) did not affect their blood sugar levels (Table II).

In Fig. 6 are shown the data obtained following the oral administration of leucine for Patient 1 (J. C.) at 20 months of age and for Patient 2 (R. L.) at 34 months of age. The dose employed was twice (150 mg. per kilogram) that employed in the intravenous testing procedure (75 mg. per kilogram) and corresponds to that used by Cochrane and associates.[1] The test on Pa-

tient 1 (J. C.) was interrupted by the intravenous administration of glucose to control a convulsion.

**Urinary studies.** No abnormal aminoaciduria was found in either patient by paper chromatographic examination of random urine specimens on repeated occasions. The alpha-amino nitrogen content of a 24-hour urine specimen was 62 mg. in Patient 1 (J. C.) at 19 months of age and 127 mg. in Patient 2 (R. L.) at 30 months of age. These values are within the normal range for our laboratory. Benedict's test and paper chromatographic examinations for sugar in urines of both patients were repeatedly negative. Several random urine specimens from each patient were examined grossly for keto acids by the addition of 2, 4-dinitrophenylhydrazine. No precipitate formed, thus indicating absence of excessive quantities of carbonyl-containing compounds.

**Family studies.** The family of Patient 1 (J. C.) has been studied in a preliminary fashion. The mother of this patient had a glucose tolerance test in another hospital on the second postpartum day because her infant weighed 9 pounds and the clinical course was similar to that of an infant of a "prediabetic" mother. The results are shown in Fig. 7. This glucose tolerance test was interpreted as being consistent with diabetes mellitus. Six months later we tested this mother separately with standard and cortisone-modified glucose tolerance tests. These data are also given in Fig. 7. Although the cortisone-modified test shows a relatively decreased tolerance to glucose as compared to the standard test, both tests are within normal limits.[14] Her blood glucose response to orally administered leucine was tested at dosage levels of 20, 50, and 150 mg. per kilogram, respectively, and was found to be normal in each instance.

The father of the patient was also studied. The standard glucose tolerance test showed the following blood sugar levels: fasting, 78; at 30 minutes, 150; at 1 hour, 171; at 2 hours, 124; and at 3 hours, 64 mg. per cent, respectively. He was tested three times by the oral administration of leucine in increasing doses (15, 50, and 100 mg. per kilogram). These results (Fig. 8) are sug-

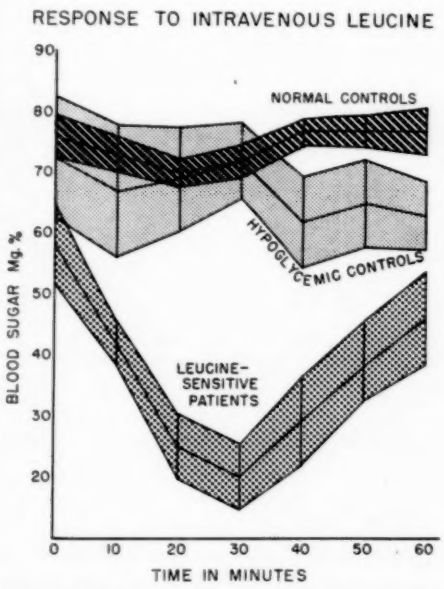


**Fig. 5.** The data used to obtain the mean values in Table II are depicted graphically. The mean and plus and minus one standard error of the mean are included within the shaded areas.

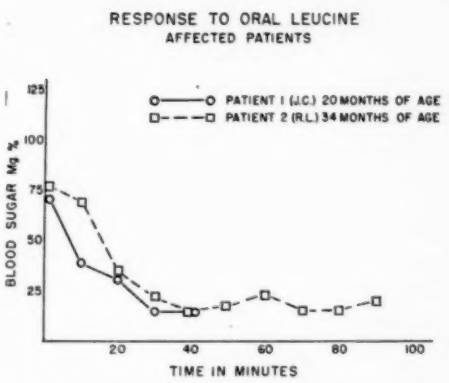


**Fig. 6.** Oral leucine tolerance test. Leucine (150 mg. per kilogram) administered by gavage within a 5-minute period 2 hours postprandially. The test on Patient 1 (J. C.) was interrupted by the intravenous administration of glucose at 40 minutes because he had a convulsion. Note the prolonged hypoglycemia in Patient 2 (R. L.) and compare it with the short period of hypoglycemia after intravenously administered leucine as shown in Fig. 5.

**Table II.** Intravenous leucine (75 mg. per kilogram)

| | | *Blood sugar response in mg. % (time in minutes)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Age in months* | *0* | *10* | *15* | *20* | *30* | *40* | *50* | *60* |
| *Leucine-sensitive patients.* | | | | | | | | | |
| J. C. | 7 (on ACTH) | 45 | 30 | 14 | 11 | 3 | 9 | 18 | |
| | 9 (on ACTH) | 59 | 42 | | 30 | 33 | 50 | 63 | 58 |
| | 17 | 65 | 50 | | 43 | 29 | 35 | 43 | 42 |
| | 17 (100 mg./Kg.)* | 64 | | 28 | | 43 | 50 | | 61 |
| | 19 | 68 | | 49 | | 38 | | | 67 |
| | 20† | 130 | 73 | | 52 | 49 | 58 | 53 | 52 |
| R. L. | 29 | 50 | 48 | | 24 | 20 | 17 | 33 | |
| | 31 (100 mg./Kg.)* | 44 | | 15 | | 12 | 19 | | 23 |
| | 32 | 37 | | 10 | | 16 | | | 38 |
| | 34 | 59 | 41 | | 19 | 3 | 32 | 32 | 23 |
| Mean | | 58 | 42 | 24 | 25 | 20 | 29 | 38 | 46 |
| S.E.M. | | 6.2 | 3.7 | | 5.4 | 5.3 | 7.2 | 7.5 | 7.7 |
| *Hypoglycemic control patients.* | | | | | | | | | |
| J. S. | 1 | 62 | 68 | | 62 | 62 | 48 | 51 | 53 |
| J. S. | 2 | 57 | | 57 | 52 | 54 | 61 | 53 | 61 |
| J. D. | 21 | 28 | 19 | | 33 | 45 | 25 | 38 | 36 |
| K. McL. | 32 | 65 | 66 | | 65 | 72 | 66 | 66 | 65 |
| J. B. | 33 | 133 | 92 | | 100 | 98 | | 93 | |
| S. W. | 38 | 84 | 69 | | 89 | 87 | 73 | 81 | 81 |
| R. D. | 46 | 68 | | 90 | | 78 | 80 | | 75 |
| J. Z. | 59 | 83 | 91 | | 85 | 79 | 79 | 74 | 71 |
| Mean | | 72.5 | 67 | | 69 | 72 | 62 | 65 | 63 |
| S.E.M. | | 10.4 | 10.9 | | 8.8 | 6.2 | 7.4 | 7.2 | 5.6 |
| *Normal control patients.* | | | | | | | | | |
| C. R. | 2 | 71 | 82 | | 79 | 69 | 72 | 77 | 78 |
| R. S. | 3 | 79 | 73 | | 68 | 78 | 74 | 77 | 76 |
| J. V. | 3 | 63 | 62 | | 68 | 57 | 72 | 74 | 73 |
| W. McM. | 4 | 66 | 74 | | 68 | 66 | 81 | 80 | 63 |
| A. E. | 19 | 96 | | 90 | | 87 | 86 | | 92 |
| T. V. | 24 | 68 | 68 | 69 | | 73 | 73 | 87 | 73 |
| L. S. | 27 | 87 | | 70 | | 80 | | | |
| L. S. | 27 (100 mg./Kg.)* | 58 | | 56 | | 60 | | 79 | 71 |
| L. J. | 38 | 73 | | | | 72 | | | 70 |
| M. S. | 42 | 77 | 79 | | 67 | 67 | 80 | 68 | 93 |
| Mean | | 76 | 73 | | 70 | 72 | 77 | 77 | 77 |
| S.E.M. | | 3.5 | 3.0 | | 2.3 | 2.9 | 2.1 | 2.6 | 3.7 |

*Not included in mean because of the high dose of leucine.

†These data not included in the means because the fasting blood sugar level was more than three standard deviations greater than the mean calculated without it. Three subsequent fasting blood sugar values in this patient on different days at 21 months of age were 64, 69, and 70 mg. per cent, respectively.

gestive of leucine sensitivity. The full dose of 150 mg. per kilogram has not yet been used since the subject experienced faintness and dizziness with the largest dose and has refused further testing.

There are 2 male siblings of Patient 1 (J. C.) who are apparently normal and exhibit fasting blood sugar levels of 71 and 58 mg. per cent, respectively. No other studies have been performed on this family to date.

## DISCUSSION

Hypoglycemia in infancy and childhood often escapes clinical detection for an unduly long interval after the onset of symptoms. When the presence of hypoglycemia is established, there remains the more dif-

fficult problem of establishing its etiology. A number of causes of hypoglycemia are known; they include tumors and hyperplasia of the islet cells, hepatic disease, glycogen storage disease, anterior pituitary or adrenocortical hypofunction, central nervous system disorders, poisoning, and others. Transient hypoglycemia in the neonatal period also occurs in some infants of diabetic mothers,[13] in prematurely born infants,[15] and occasionally in infants born to mothers who have toxemia of pregnancy.[16] Despite the many entities that are at present known to produce, or to be associated with, hypoglycemia, the etiological factors responsible for the majority of cases in infancy and childhood are yet to be delineated.

The observation by Cochrane, Payne, Simpkiss, and Woolf[1] that some hypoglycemic patients are sensitive to leucine has been a major impetus to the further study of this problem. More recently, Broberger, Jungner, and Zetterström[17] have reported their experiences with 3 children with idiopathic hypoglycemia who failed to respond with the expected increase of epinephrine excretion when hypoglycemia was induced by the intravenous injection of insulin. This observation may lead to the segregation of another group of patients from those now designated as having idiopathic hypoglycemia.

The proportion of patients with hypoglycemia who are leucine sensitive is not known at this time. Two out of 9 patients with hypoglycemia tested by us by the intravenous administration of L-leucine have been sensitive. Cochrane[2] observed "a significant lowering" of blood sugar levels in 4 of 11 infants with idiopathic infantile hypoglycemia by the oral administration of casein hydrolysate and/or L-leucine. Ulstrom and Sanfilippo[3] tested 7 children by the oral administration of L-leucine and casein separately and 3 additional children by casein alone. Four of these hypoglycemic children showed "definite decreases" in blood sugar levels following ingestion of L-leucine and of casein. From these limited data, it appears that perhaps as many as one third of all infants with idiopathic hypoglycemia may be leucine sensitive.

The oral administration of casein or of L-leucine or the intravenous administration of L-leucine all appear equally competent in producing hypoglycemia in sensitive patients. The superiority for diagnostic purposes of one testing substance over another, or of one route of administration over another, remains to be determined. The intra-

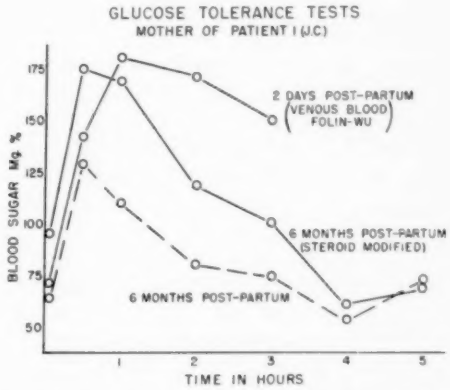


**Fig. 7.** The glucose tolerance test performed 2 days post partum was obtained in another hospital with the use of venous blood and the Folin-Wu method. The steroid modified glucose tolerance test was performed according to the method of Conn.[14]

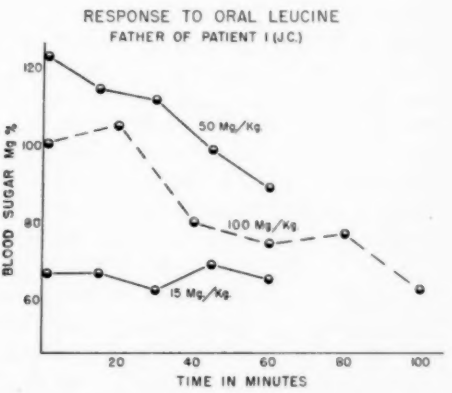


**Fig. 8.** Venous blood was utilized for the blood sugar determinations in the above tests. Note that the largest dose of leucine administered was only 100 mg. per kilogram.

venous test described in this report was devised in an effort to eliminate the variables attendant on gastrointestinal absorption and in the hope of obtaining more reproducible results. The dose used for the intravenous testing procedure (75 mg. per kilogram) is one-half that generally used for the oral testing procedure (150 mg. per kilogram). With the intravenous testing procedure the individual is usually subjected to hypoglycemia for a shorter time than with the oral administration of casein or leucine. However, the oral administration of leucine, being more comparable to the oral feeding of proteins, may more nearly mimic the usual clinical pattern. It may be noted that the only seizures precipitated by leucine testing by us followed its oral administration.

It has been reported that normal children show no change in blood sugar levels following the oral administration of leucine.[2] From perusal of our data, however, it appears that there may be a discernible decline in blood sugar levels following the intravenous administration of L-leucine to normal children (Fig. 5). This is especially apparent when one compares this decline in blood sugar level to the slight elevation in another group of normal children who have had no manipulation other than the drawing of blood samples. The collection of additional data are in progress in order to test the validity of this observation.

One of the most difficult problems related to the child with severe hypoglycemia is the decision concerning surgical exploration for an islet cell adenoma. The demonstration of leucine sensitivity might help the clinician to exclude the presence of functioning islet cell tumors, but this remains to be established. It would be essential to demonstrate that patients with functioning islet cell adenomas are not leucine sensitive before this test procedure would become useful in the differential diagnostic evaluation. A 4-year-old child with a functioning islet cell tumor observed by Hartmann and associates[7] was not leucine sensitive, nor was an adult male with an islet cell adenoma studied by Overstreet.[18] On the other hand, Schwartz, Flanagan, Stupp[illegible]y, and Tarum[19] reported the cases of a 3[illegible]-year-old woman with a functioning pancr[illegible]atic islet cell adenoma and a 76-year-o[illegible]d woman with a functioning pancreatic ca[illegible]cinoma, whom they thought to be leucine sensitive. In the patient with the adenoma, hypoglycemia and leucine sensitivity were no longer demonstrable following surgical removal of the tumor. The details of these authors' studies have not been published as of this writing and it is difficult to evaluate their observations.

To our knowledge there has only been one autopsy of a leucine-sensitive patient.[20] The islets appeared "large and hyperplastic" but detailed studies of the tissues are not yet available. Cochrane and co-workers[1] studied the histologic appearance of the pancreas in surgically obtained material from 2 of their patients. One showed no significant pathologic changes, but in the other there were about 4 times the normal number of islet cells. The finding of islet cell hyperplasia in 2 of 3 leucine-sensitive patients whose pancreata have been examined histologically causes one to speculate on its frequency in these patients.

We were unable to study completely the parents of our 2 patients. Patient 2 (R. L.) was an illegitimate child and it was not feasible to study the mother. The mother of Patient 1 (J. C.) was not leucine sensitive. The father of this child when tested orally with increasing doses of leucine demonstrated a definite decline in blood sugar level. The largest test dose used was only 100 mg. per kilogram which is two thirds of the usual oral test dose. Since he experienced dizziness and weakness during and after the test, he refused to be subjected to further testing. He has at no other time had any symptoms suggestive of hypoglycemia. In Cochrane's[1] original report the 27-year-old father of 2 affected children was leucine sensitive. A second leucine-sensitive parent of an affected child was subsequently described by Cochrane and Moya.[4] Both of these parents had seizures in infan[illegible]y. Schubert[21] has reported the case of an

affected child whose 40-year-old mother demonstrated a "typically positive leucine test." This mother "gave a history of convulsions in childhood" but is "normal mentally and has no seizures at present." Although leucine sensitivity appears to be genetically determined, it is not possible to infer the mode of inheritance from the available data. In view of the paucity of symptoms in the affected parents, they could be heterozygous carriers of a recessive gene for the disorder. A dominant mode of inheritance with variable penetrance and/or expressivity cannot be excluded.

A rational form of therapy would be based on a knowledge of the pathogenesis of the disorder. In the absence of this, therapy is at best empiric. Cochrane and Moya[4] have suggested the administration of carbohydrate 20 to 30 minutes after feeding to counteract the effect of the protein in lowering the blood sugar level. The administration of a diet low in leucine appears rational, were not leucine an essential amino acid. The minimal daily requirement of leucine for growth is 150 to 229 mg. per kilogram.[22] An inquiry into the amino acid content of various milk preparations is instructive. Human milk contains only approximately 40 per cent as much leucine as cow's milk on an isocaloric basis (Table III). Many of the artificial milk preparations approach human milk in their leucine content when compared on an isocaloric basis, because the protein content of prepared milks simulates that of human milk. It appears that human milk or a prepared milk with an equally low leucine content should be preferable to undiluted cow's milk. As can also be seen in Table III, high protein milks contain a high leucine content on an isocaloric basis.

Corticotropin and the adrenal cortical steroids have been used as an adjunct to therapy in this disorder. Some workers have suggested that corticotropin is superior to the adrenal cortical steroids. The evidence for this appears tenuous. In fact, we are skeptical that either is very effective in this disorder. Patient 1 (J. C.) was treated with corticotropin in sufficient dosage and for a sufficient time to induce a severe Cushingoid state. In spite of this, the child continued to have hypoglycemic attacks and to have leucine sensitivity, although he appeared somewhat improved clinically. The rationale for glucocorticoid therapy in patients with hypoglycemia is based on its gluconeogenic action. One of the other actions of glucocorticoids, however, is to accelerate catabolism of proteins and thus to increase the levels of circulating free amino acids.[23] The latter effect may in part counteract the former and might explain our poor results in the management of Patient 1 (J. C.) with corticotropin.

With the limited experience in the management of this disorder, the best that can be recommended for therapy is the administration of a diet containing the minimal requirement of leucine, and the feeding of glucose water 20 to 40 minutes after meals. The desirability of adding corticotropin or adrenal cortical steroids to this regimen remains to be established.

The mechanism by which leucine, an essential amino acid, may alter carbohydrate metabolism in certain individuals to such a profound degree as to produce severe hypoglycemia is at present unknown. We are

**Table III.** L-Leucine content in milligrams per 100 ml. of 20 Cal. per ounce milk or formula

| | |
|---|---|
| Alacta | 457 |
| Baker's modified | 238 |
| Bremil | 156 |
| Cow | 356 |
| Enfamil | 164 |
| Human | 161 |
| Lactum | 295 |
| Mull-Soy | 220 |
| Nutramigen | 265 |
| Olac | 369 |
| Powdered protein milk | 514 |
| Similac | 181 |
| S-M-A | 157 |
| Sobee | 225 |
| Varamel | 270 |

Data for the prepared milks were supplied by the respective processing companies. Data for bovine and human milk is from W. S. Spector, editor: Handbook of Biological Data, Philadelphia, 1956, W. B. Saunders Company.

currently investigating some of the biochemical aspects of this problem and data bearing on one phase are presented in the following paper.[24]

## SUMMARY

Two infants with leucine-sensitive hypoglycemia are presented. A standard intravenous leucine tolerance test has been devised and utilized in the study of these 2 infants and of euglycemic and other hypoglycemic children who were not leucine sensitive. The leucine-sensitive children consistently had a decline in blood sugar levels of greater than 50 per cent 20 to 40 minutes after administration of the leucine. The diagnosis of leucine-sensitive hypoglycemia and management of infants who have it are discussed.

The authors are indebted to Dr. Helen S. Reardon for the early management of Patient 1 (J. C.) as well as for advice and consultation, and to Dr. William Neth and Dr. James Weeks of the Delaware Memorial Hospital, Wilmington, Delaware, for referring Patient 2 (R. L.) and for making available to us the records on this patient. We also wish to acknowledge the technical assistance of Mary Lou Bauman and Pasquale Pellecchia.

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# Leucine-induced hypoglycemia

## II. Studies concerning other amino acids and leucine metabolites

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IN ADDITION TO L-leucine, a number of other amino acids have been tested for their effect on blood sugar levels in patients with "leucine-sensitive hypoglycemia." Neither L-tyrosine[1] nor glycine or L-tryptophan[2] had any effect. On the other hand, it has been reported that DL-isoleucine, DL-valine, and L-valine caused "the blood sugar to fall in the same period of time" as that observed with L-leucine.[3] D-leucine also had a hypoglycemic effect in patients with this disorder.[2] More recently L-isoleucine and L-valine have been shown to produce hypoglycemia in a patient with this disorder.[4] However, the systematic study of all of the naturally occurring amino acids in patients with leucine-sensitive hypoglycemia has not been reported.

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Isovaleric acid, a catabolic product of leucine, was also found to produce a hypoglycemic effect,[1, 5] and it was suggested that there might be a defect in the catabolism of leucine in this disorder and that the isovaleric acid might, in fact, be the hypoglycemic agent. This line of investigation has been pursued further by Hartmann and coworkers[6] who administered three further catabolic products of leucine (beta-methyl beta-hydroxyglutaric acid, beta-methylcrotonic acid, and potassium acetoacetate) (Fig. 1).

In Part I of this report[7] the case histories and clinical studies of 2 infants with leucine-sensitive hypoglycemia were presented. In this paper additional studies designed to elucidate the specificity of the hypoglycemic effect of leucine and its mode of action are reported. The clinical and blood sugar responses in this disorder were observed following the rapid intravenous injection of the naturally occurring L-amino acids, D-leucine, isovaleric acid, and alpha-ketoisocaproic acid. Urinary monocarboxylic keto acids were measured following separate intravenous loading with L-leucine and alpha-ketoisocaproic acid, respectively. Finally, blood insulin levels were measured following administration of L-leucine.

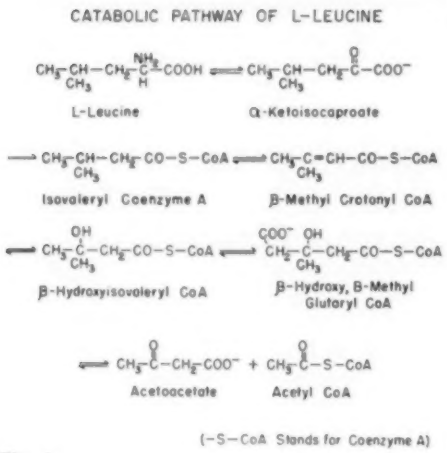


Fig. 1.

## METHODS OF STUDY

**A. Amino acids.** The method for preparation of the solution of L-leucine for intravenous administration has been presented in the preceding paper.[7] Sixteen other L-amino acids and D-leucine were prepared in a similar manner. In addition to the amino acids tested by the intravenous route, tryptophan and tyrosine, owing to their relative insolubility, were administered as a slurry by gavage in doses three times those used for the other amino acids. Chromatographically pure amino acids and their hydrochlorides were used.* The pH of the solution was adjusted to 7.0 before sterilization.

A test dose was chosen which would be equimolar to that used for the leucine (75 mg. per kilogram is equivalent to 0.57 millimoles per kilogram). Depending upon the solubility of the amino acids, the amount of solution administered varied from 2 to 3.7 ml. per kilogram. Four of the amino acids were given as a group, six others in groups of two each, and the remainder individually. The various amino acids, in groups or individually, were always tested for possible toxicity in rats prior to their administration to children. No ill effects were noted when 10 to 20 times the dose per kilogram normally used was injected intraperitoneally.

**B. Catabolic products of L-leucine.** Isovaleric acid and alpha-ketoisocaproic acid* were prepared for intravenous use and administered in the same manner and at the same dose as that described for leucine and other amino acids. In order to avoid possible decarboxylation of the alpha-ketoisocaproic acid during sterilization it was usually prepared by the addition of a previously weighed sample to a calculated volume of sterile dilute sodium hydroxide.

**C. Loading tests.** A known quantity of either L-leucine or alpha-ketoisocaproic acid (100 mg. per kilogram) was injected intravenously on different days and urine was collected during the subsequent 2 hour period for measurement of the monocarboxylic keto-acids. The normal excretion of total monocarboxylic keto-acids was measured during a comparable 2 hour control period. Monocarboxylic acids in the urine were measured by a modification of the method described by Friedemann,[8] in which the 2,4-dinitrophenylhydrazone is made, extracted into benzene, re-extracted into bicarbonate, made alkaline with sodium hydroxide, and the optical density measured in a Zeiss spectrophotometer at 475 mμ. Alpha-ketoisocaproic acid was used as the standard.

For both the affected and control patients, the test period for measuring the blood sugar responses to the various compounds usually began 2 hours following the first regular morning feeding. The natural decline of the blood sugar level during the test period from the second to the third postprandial hour was determined on repeated occasions.[7]

*All the amino acids used were obtained either from Mann Research Laboratories, Inc., New York, N. Y., or from California Corporation for Biochemical Research, Los Angeles, Calif.

*Isovaleric acid (95 per cent pure beta-methylbutyric acid) and alpha-ketoisocaproic acid (99 per cent pure, prepared by enzymatic oxidation of L-leucine) were obtained from and analyzed by K & K Laboratories, Inc., Jamaica, N. Y.

**Table I.** Intravenous amino acids (0.57 mM. per kilogram)

| L-amino acids | Subject | Blood sugar response in mg. % (time in minutes) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 10 | 15 | 20 | 30 | 40 | 45 | 50 | 60 |
| Isoleucine | Patient 1 (J. C.) | 72 | 68 | – | 59 | 54 | 44 | – | 44 | 50 |
| | Patient 1 (J. C.) | 122 | 113 | – | 104 | 95 | 90 | – | 98 | 90 |
| | Patient 2 (R. L.) | 64 | 57 | – | 55 | 53 | – | 51 | 50 | 60 |
| | Control 1 (L. S.) | 76 | – | 81 | – | 66 | – | 65 | – | 71 |
| | Control 2 (A. E.) | 80 | – | 58 | – | 69 | – | 72 | – | 76 |
| | Control 3 (D. G.) | 94 | 87 | – | 79 | 100 | 107 | – | 94 | 83 |
| Alanine, glycine, proline, and hydroxyproline | Patient 1 (J. C.) | 92 | – | 76 | – | 68 | – | 53 | – | 51 |
| | Patient 2 (R. L.) | 44 | – | 29 | – | 24 | – | 28 | – | 35 |
| | Patient 2 (R. L.) | 45 | – | 54 | – | 46 | – | 65 | – | 49 |
| | Control 1 (L. S.) | 95 | – | 54 | – | 78 | – | 82 | – | 115 |
| | Control 2 (A. E.) | 80 | – | – | 75 | 68 | – | 82 | – | 73 |
| Tryptophan and tyrosine* | Patient 1 (J. C.) | 62 | – | – | 63 | – | 65 | – | – | 66 |
| | Patient 2 (R. L.) | 41 | – | – | 45 | – | 81 | – | – | – |
| | Control 1 (L. S.) | 56 | – | – | 84 | – | 74 | – | – | 69 |
| | Control 2 (A. E.) | 49 | – | – | 84 | – | 81 | – | – | 81 |
| Aspartic and glutamic acids | Patient 1 (J. C.) | 48 | – | 59 | – | 46 | – | 46 | – | 41 |
| | Patient 2 (R. L.) | 71 | – | 104 | – | 67 | – | 60 | – | 56 |
| | Control 1 (L. S.) | 94 | – | 94 | – | 79 | – | 75 | – | 72 |
| | Control 2 (A. E.) | 73 | – | – | 66 | 68 | – | – | 79 | 67 |
| Arginine and lysine | Patient 1 (J. C.) | 66 | – | 64 | – | 65 | – | 74 | – | 72 |
| | Patient 2 (R. L.) | 64 | – | 58 | – | 52 | – | 45 | – | 44 |
| | Control 1 (L. S.) | 52 | – | 38 | – | 38 | – | 64 | – | 70 |
| Histidine | Patient 1 (J. C.) | 59 | – | 50 | – | 63 | – | 61 | – | 62 |
| | Patient 2 (R. L.) | 51 | – | 43 | – | 37 | – | 36 | – | 36 |
| | Control 1 (L. S.) | 88 | – | 94 | – | 83 | – | 90 | – | 89 |
| Serine and threonine | Patient 1 (J. C.) | 76 | – | 50 | – | 63 | – | 58 | – | 46 |
| | Patient 2 (R. L.) | 76 | – | 41 | – | 60 | – | 64 | – | 72 |
| | Control 1 (L. S.) | 95 | – | 56 | – | 47 | – | 44 | – | 63 |
| Serine | Patient 1 (J. C.) | 95 | 69 | – | 89 | 81 | – | – | 75 | 91 |
| | Patient 1 (J. C.) | 79 | 53 | – | 55 | 57 | 70 | – | 78 | 69 |
| | Patient 2 (R. L.) | 71 | 43 | – | 44 | 55 | – | 65 | – | 66 |
| | Control 3 (D. G.) | 81 | 93 | – | 92 | 92 | 90 | – | 92 | 93 |
| | Control 4 (M. O.) | 82 | 78 | – | 83 | 91 | 91 | – | 90 | 91 |
| Threonine | Patient 1 (J. C.) | 57 | 60 | – | 61 | 68 | – | 73 | – | 70 |
| | Patient 2 (R. L.) | 55 | 52 | – | 48 | 49 | – | 42 | – | 50 |
| Valine | Patient 1 (J. C.) | 73 | – | 60 | – | 62 | – | 55 | – | 51 |
| | Patient 1 (J. C.) | 79 | 53 | – | 55 | 57 | 70 | – | 78 | 69 |
| | Patient 2 (R. L.) | 76 | – | 62 | – | 64 | – | 97 | – | 71 |
| | Patient 2 (R. L.) | 53 | – | 34 | – | 28 | – | 32 | – | 36 |
| | Control 1 (L. S.) | 125 | – | 78 | – | 55 | – | 55 | – | 98 |
| | Control 3 (D. G.) | 85 | 83 | – | 83 | 83 | 90 | – | 93 | 90 |
| | Control 4 (M. O.) | 94 | 93 | – | 96 | 94 | 90 | – | 89 | 90 |
| Methionine | Patient 1 (J. C.) | 85 | – | 68 | – | 62 | – | 66 | – | 65 |
| | Patient 2 (R. L.) | 41 | – | 31 | – | 36 | – | 38 | – | 41 |
| | Control 1 (L. S.) | 75 | – | 58 | – | 87 | – | 98 | – | 75 |
| Phenylalanine | Patient 1 (J. C.) | 67 | – | 52 | – | 62 | – | 61 | – | 67 |
| | Patient 2 (R. L.) | 43 | – | – | – | 50 | – | 49 | – | 43 |
| | Control 1 (L. S.) | 88 | – | 91 | – | 79 | – | 75 | – | 74 |

*Administered by gavage at three times the above stated dose. Patient 2 (R. L.) vomited after 20 minutes.

## RESULTS

**A. L-amino acids.** None of the amino acids, administered singly or in groups, had an effect which was as unequivocal as that produced by leucine (Table I). On the other hand, three of the amino acids tested (isoleucine, valine, and serine) did appear to produce a significant degree of hypoglycemia in isolated instances. None of the other amino acids produced a hypoglycemic response which was significantly greater than that seen in a comparable control period during which no amino acid was administered.[7]

Isoleucine produced only a moderate response in Patient 1 (J. C.) and no significant response in Patient 2 (R. L.). Valine had a definite effect on Patient 2 (R. L.) which was not demonstrated upon repetition of the test 3 weeks later. In Patient 1 (J. C.) valine produced no effect greater than the blood sugar decline noted in the control period. On a second occasion no significant effect was seen until 50 minutes had elapsed. One of the 3 control patients showed a hypoglycemic effect following administration of valine which was greater than that demonstrated in either patient.

Initially, serine and threonine were tested together. Since the responses obtained in both patients were suggestive of an effect, the two amino acids were tested separately at a later date. Threonine had no effect. Serine produced a significant effect in Patient 2 (R. L.), no effect in Patient 1 (J. C.) on one occasion, and a moderate effect on a second occasion. As with valine, the combination of serine and threonine produced a marked lowering of the blood sugar levels in the control patient. Serine alone had no effect on 2 other control patients.

**B. D-leucine.** D-leucine was administered intravenously at a dose of 0.57 mM. per kilogram and orally at a dose of 2.28 mM. per kilogram. Neither the control nor the affected patients had any untoward reactions. The blood sugar responses are given in Table II. In Patient 1 (J. C.) the oral administration of D-leucine resulted in a definite hypoglycemic response almost as great as that produced by L-leucine. The intravenous administration of the D-leucine produced a less marked response. In Patient 2 (R. L.) the results were markedly different. D-leucine had a definite hypoglycemic effect when given intravenously but failed to alter the blood sugar level when given orally.

**C. Catabolic products of L-leucine.**

*1. Isovaleric acid.* Isovaleric acid was tested nine times in the 2 affected patients and once in each of 2 control patients (Table III). Oral administration of this compound on three occasions at doses two to four times the intravenous dose was without effect on blood sugar levels. Isovaleric acid was administered intravenously to the affected patients six times; during five of these tests there was no decrease in blood sugar levels. In fact, there appeared to be a small increase in blood sugar levels immediately following administration of the test compound. On only one occasion did the blood sugar level fall, but in this instance the fasting blood sugar level was higher than usual. There were no untoward reac-

**Table II.** Blood sugar responses to D-leucine

| *Patient* | *Route* | *Dose in mM./Kg.* | *Age in months* | *Blood sugar response in mg. % (time in minutes)* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *0* | *15* | *30* | *45* | *60* | *75* | *90* | *120* |
| J. C. | Intravenous | 0.57 | 16 | 51 | 43 | 39 | 43 | 41 | | | |
| J. C. | Oral | 2.28 | 17 | 52 | 47 | 33 | 38 | 40 | 31 | 38 | 42 |
| R. L. | Intravenous | 0.57 | 29 | 50 | 33 | 31 | 35 | 29 | | | |
| R. L. | Oral | 2.28 | 30 | 51 | 52 | 56 | 57 | 60 | 64 | 63 | 64 |
| Control | | | | | | | | | | | |
| L. S. | Intravenous | 0.57 | 25 | 71 | 76 | 82 | 98 | 92 | | | |

tions in any of the patients, except for an inconstant, transient flush reaction at the time of injection.

*C. Alpha-ketoisocaproic acid.* Alpha-ketoisocaproic acid was tested six times in the 2 affected patients and three times in the 2 control subjects (Table IV). In Patient 1 (J. C.) this compound produced a hypoglycemic response on two of the 4 occasions comparable to that produced by leucine. On two other occasions the response was minimal (Fig. 2). In Patient 2 (R. L.) the alpha-ketoisocaproic acid on both occasions produced a definite hypoglycemic effect (Fig. 3). Of the 2 control subjects tested, a moderate hypoglycemic effect was observed on one of three occasions. The alpha-ketoisocaproic acid occasionally produced irritability, much the same as did the leucine, in the affected patients but had no discernible effect on the control patients.

**D. Loading tests.** Because alpha-ketoisocaproic acid usually produced a decrease in blood sugar levels when administered to affected patients, it appeared reasonable to look for a defect in the further metabolism of this compound. Since examination of random urine specimens did not show excess keto-acids,[7] the patients were given a leucine or alpha-ketoisocaproic acid load and urines were examined quantitatively for alpha–keto-acids.

The results of this study are shown in Table V. The total amount of alpha–keto-acids recovered in the urine of the 2 affected patients after loading with either compound was not significantly greater than that observed with a control patient. The amount of leucine recovered as keto-acids was less than 1 per cent of the administered dose.

When alpha-ketoisocaproic acid was administered, the total amount of keto-acids recovered in 2 hours ranged between 3 and 7 per cent of the administered dose. The major portion of the keto-acids was excreted in the first 30 minutes after administration of the test compound. The keto-acid recovered from the urine as the 2,4-dinitrophenylhydrazone was identified as alpha-ketoisocaproic acid by its melting point (158° to 160° C.). Admixture of this derivative with authentic alpha-ketoisocaproic 2,4-dinitrophenylhydrazone did not result in any change of the melting point.

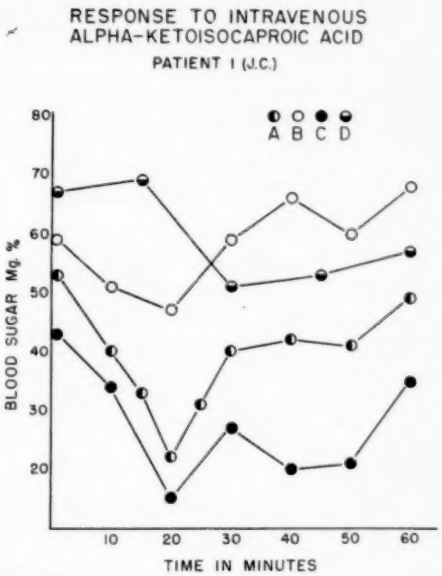


**Fig. 2.**

*A*, Age, 10 months; dose, 0.46 mM. per kilogram.

*B*, Age, 14 months; dose, 0.46 mM. per kilogram.

*C*, Age, 15 months; dose, 0.57 mM. per kilogram.

*D*, Age, 15 months; dose, 0.77 mM. per kilogram.

During the test periods the patients exhibited the usual hypoglycemic responses.

## DISCUSSION

None of the eighteen L-amino acids administered induced a depression of blood sugar levels which was as definitive as that produced by L-leucine. L-isoleucine, L-valine, and L-serine did occasionally have an effect. In contrast to the reproducible effect noted with L-leucine, however, these amino acids produced effects which were not reproducible from time to time in the same patient nor at the same time in both patients. Moreover, administration of valine was associated with a definite fall in blood sugar levels in

**Table III.** Blood sugar responses to isovaleric acid

| *Patient* | *Route* | *Dose in mM./Kg.* | *Age in months* | *Blood sugar response in mg. % (time in minutes)* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *0* | *10* | *15* | *20* | *30* | *40* | *45* | *50* | *60* | *70* |
| J. C. | Intravenous | 0.57 | 15 | 42 | 62 | | 52 | 45 | 35 | | | 31 | |
| J. C. | Intravenous | 0.57 | 17 | 75 | | 90 | | 52 | | 53 | | 59 | |
| J. C. | Intravenous | 0.57 | 17 | 79 | 86 | | 95 | 66 | 68 | | 65 | 65 | |
| J. C. | Oral | 1.2 | 10 | 59 | 56 | | 53 | 50 | | | 46 | 43 | 49 |
| J. C. | Oral | 2.4 | 10 | 51 | 46 | | 55 | 57 | 50 | | | 60 | 56 |
| R. L. | Intravenous | 0.57 | 29 | 46 | 50 | | 54 | 59 | 53 | | | 32 | |
| R. L. | Intravenous | 0.57 | 31 | 102 | | 86 | | 64 | | 63 | | 39 | |
| R. L. | Intravenous | 0.57 | 31 | 53 | 61 | | 46 | 51 | 42 | | 47 | 51 | |
| R. L. | Oral | 1.2 | 31 | 59 | | 64 | | 61 | | 50 | | 56 | 61 |
| Controls | | | | | | | | | | | | | |
| A. E. | Intravenous | 0.57 | 25 | 84 | | 75 | | 73 | | 82 | | 101 | |
| L. S. | Intravenous | 0.57 | 19 | 90 | | 73 | | 89 | | 79 | | 69 | |

**Table IV.** Blood sugar responses to intravenous alpha-ketoisocaproic acid

| *Patient* | *Dose in mM./Kg.* | *Age in months* | *Blood sugar response in mg. % (time in minutes)* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | *0* | *10* | *15* | *20* | *25* | *30* | *40* | *45* | *50* | *60* |
| J. C. | 0.46 | 10 | 53 | 40 | 33 | 22 | 31 | 40 | 42 | | 41 | 49 |
| J. C. | 0.46 | 14 | 59 | 51 | | 47 | | 59 | 66 | | 60 | 68 |
| J. C. | 0.57 | 15 | 43 | 34 | | 15 | | 27 | 20 | | 21 | 35 |
| J. C. | 0.77 | 15 | 67 | | 69 | | | 51 | | 53 | | 57 |
| R. L. | 0.57 | 29 | 60 | 50 | 43 | 36 | | 27 | 35 | | 47 | 58 |
| R. L. | 0.77 | 30 | 72 | | | 44 | | 35 | | 46 | | 28 |
| Controls | | | | | | | | | | | | |
| L. S. | 0.38 | 25 | 95 | 77 | | 71 | | 70 | | 88 | | 93 |
| L. S. | 0.77 | 26 | 76 | | 71 | | | 68 | | 78 | | 87 |
| A. E. | 0.57 | 19 | 64 | 77 | 81 | 78 | | 77 | 75 | | 87 | 88 |

**Table V.** Monocarboxylic keto-acids in urine expressed as milligrams of alpha-ketoisocaproic acid per sample

| | *Amount administered intravenously in mg.* | *Amount excreted in interval shown (minutes)* | | | | *Total amount recovered in 2 hours* | *% recovered in 2 hours** |
|---|---|---|---|---|---|---|---|
| | | *0-30* | *30-60* | *60-90* | *90-120* | | |
| *Patient 1 (J. C.)* | | | | | | | |
| Control period | 0 | – | – | – | – | 0.5 | – |
| L-leucine | 680 | 0.2 | 0.2 | 0.1 | 0.3 | 0.8 | < 1.0 |
| Alpha-ketoisocaproic acid | 687 | 19.9 | 2.3 | 0.2 | 0.3 | 22.7 | 3.3 |
| *Patient 2 (R. L.)* | | | | | | | |
| Control period | 0 | – | – | – | – | 3.3 | – |
| L-leucine | 1227 | 1.3 | 1.2 | 0.7 | 0.6 | 3.8 | < 1.0 |
| Alpha-ketoisocaproic acid | 1217 | 85.4 | 3.2 | 2.2 | 0.8 | 91.6 | 7.5 |
| *Control 1 (L. S.)* | | | | | | | |
| Control period | 0 | – | – | – | – | 0.7 | – |
| L-leucine | 1182 | 0.3 | 0.2 | 0.1 | 0.1 | 0.7 | < 1.0 |
| Alpha-ketoisocaproic acid | 1173 | 42.7 | 1.3 | 0.6 | 0.3 | 44.9 | 3.8 |

*Corrected for 2 hour control period.

a non–leucine-sensitive control patient. These data are somewhat at variance with two preliminary reports by other workers.[3, 4] However, the degree of reproducibility of the effect of L-amino acids other than leucine is not known to us. It would be desirable to know if sudden loading with one amino acid could result in an amino acid imbalance which might alter the leucine concentration sufficiently to result in hypoglycemia. Such a secondary effect might help explain the inconsistent results which we have obtained. Until more data are available on these and other patients, the effect of leucine in this disorder may be considered to be specific at the dose level tested.

D-leucine produced a hypoglycemic effect three out of the four times tested, twice when administered intravenously and once when given orally. Cochrane[2] also reported the efficacy of D-leucine in lowering blood sugar levels in this disorder. D-leucine may produce its effect via its conversion to L-leucine, a phenomenon known to occur in the rat.[9]

Since Cochrane and associates[1] had initially demonstrated some hypoglycemic effect of isovaleric acid in 1 leucine-sensitive patient, this compound was administered to both our patients. A hypoglycemic response was not demonstrated when this compound was administered either intravenously or orally. Patient 2 (R. L.) showed on only one occasion a slow decline in blood sugar level following administration of isovaleric acid, but the fasting blood sugar level on this occasion was higher than that usually seen in this patient.

Because the isovaleric acid did not induce hypoglycemia, alpha-ketoisocaproic acid was tested next. This compound produced hypoglycemic responses similar to those induced by L-leucine in the affected patients except that the responses were somewhat less consistent. Because of the fact that isovaleric acid did not produce hypoglycemia and alpha-ketoisocaproic acid did, we originally suggested that a defect might be present in the conversion of alpha-ketoisocaproic acid to isovaleric acid.[10] Random urine specimens from both patients were examined repeatedly for excess keto-acids, but none was found by this qualitative test as would have been expected were there a defect in leucine metabolism resulting in accumulation of alpha-ketoisocaproic acid. To test this hypothesis further, the patients were given an intravenous load, on separate days, of L-leucine or alpha-ketoisocaproic acid, respectively. The excretion of monocarboxylic keto-acids was measured in the urine within a 2 hour period after loading. Only a small fraction of the administered compounds was recovered in the urine as the monocarboxylic keto-acid. This was true in both the affected patients and in the control subject. Failure to recover abnormal amounts of alpha-keto-isocaproic acid in the urine, especially after loading, raises considerable doubt that a defect exists in the conversion of this compound to isovaleric acid in this disorder.

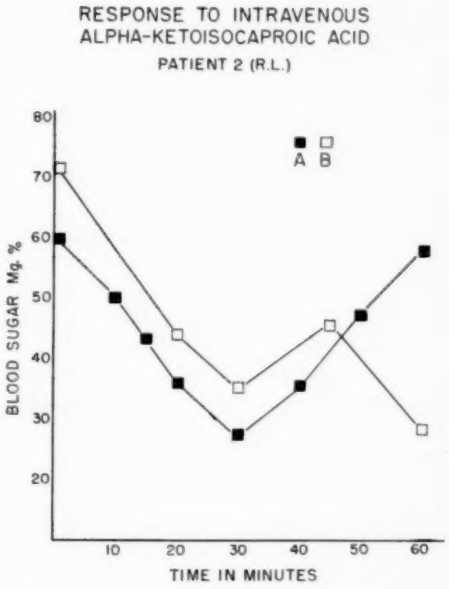


**Fig. 3.**

*A*, Age, 29 months; dose, 0.57 mM. per kilogram.

*B*, Age, 30 months; dose, 0.77 mM. per kilogram.

Hartmann, Wohltmann, Holowach, and Caldwell[6] have recently reported their experiences with the oral administration of three of the degradation products of leucine to an infant with leucine-sensitive hypoglycemia. Alpha-ketoisocaproic acid and isovaleric acid were not tested. Administration of beta-methyl, beta-hydroxyglutaric acid in a dose equivalent to 40 per cent of the standard oral dose of leucine (150 mg. per kilogram) was followed by moderate hypoglycemia. In the absence of controls, these investigators were unable to interpret this result. When the compound was given on a second occasion there was no change in the blood sugar level. Beta-methylcrotonic acid was given in a dose equivalent to 60 per cent of the standard oral leucine dose. This was also followed by a moderate fall in blood sugar level, but this response was not considered significant. When the compound was administered on a second occasion a somewhat greater hypoglycemic effect was produced. Potassium acetoacetate administration was also followed by a fall in blood sugar levels. Because of the lack of control subjects and the marked spontaneous fluctuations in blood sugar levels in the test subject, the significance of these findings is not clear.

Failure of isovaleric acid to induce hypoglycemia could possibly be due to its inability to enter the metabolic pathway since it is normally metabolized via its coenzyme A derivative.[11] At the present time it is not known whether mammalian tissue is capable of forming the coenzyme A derivatives from the free acids involved in the catabolism of L-leucine subsequent to alpha-ketoisocaproic acid. This qualification could, of course, also apply to the studies of Hartmann and co-workers.[6]

At the present time, it appears that the hypoglycemic effect induced by leucine is mediated by leucine itself and not via one of its normal degradation products. The most likely explanation for the hypoglycemic effect of alpha-ketoisocaproic acid is that it is transaminated to leucine, since this reaction is known to be reversible both in vitro[11] and in vivo.[12] The administered alpha-keto-isocaproic acid probably formed sufficient leucine to result in hypoglycemia.

These studies have not contributed to a better understanding of the mechanism by which leucine induces hypoglycemia in the susceptible individual. Preliminary in vitro studies by Cochrane and Moya,[2] using the rat hemidiaphragm, indicate that, in the presence of L-leucine, the rate of disappearance of glucose from the incubating medium is increased as much as 30 to 50 per cent. Payne and Woolf[5] reported an increased insulin-like activity in the serum of one of their leucine-sensitive patients after the oral administration of leucine. Behal and Thornton[4] have recently reported an increase in the circulating insulin level after the administration of leucine to an affected patient. We have been fortunate in obtaining the cooperation of Renold and Steinke of Boston and of Yalow and Berson of New York who have determined the level of insulin-like activity using epididymal fat and the level of insulin by an immunochemical technique, respectively. The results in the two laboratories are in gross agreement with each other. They show an increase both in insulin-like activity and in true insulin levels following intravenous administration of leucine to one of our patients.[13] Details of this investigation will be published elsewhere. Our study lends no support to the hypothesis that the primary derangement in this disorder is a defect resulting in an inability to catabolize leucine normally. At present evidence is accumulating that the decreased blood sugar levels in this disorder following leucine administration are secondary to increased circulating insulin levels. The mechanism by which this phenomenon occurs is unknown.

## SUMMARY

Two infants with leucine-sensitive hypoglycemia have been studied to elucidate the specificity and mechanism of action of L-leucine. Sixteen other naturally occurring L-amino acids have been administered intravenously and tyrosine and tryptophan by

gavage. Of these amino acids, only L-leucine consistently induced hypoglycemia. D-leucine also produced hypoglycemia when given intravenously. Alpha-ketoisocaproic and isovaleric acids were administered intravenously; the former induced hypoglycemia whereas the latter did not.

Monocarboxylic keto-acids in the urine were measured following L-leucine or alpha-ketoisocaproic acid loading. The recovery of keto-acids in the urine was of a low order, similar to that of a control subject indicating no metabolic defect in the conversion of alpha-ketoisocaproic acid to isovaleric acid.

Preliminary evidence is presented that leucine administration to affected patients results in increased circulating insulin levels.

The authors wish to acknowledge the able technical assistance of Mary Lou Baumann and Pasquale Pellecchia.

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# *A study of the biologic falsely positive reactions for syphilis in children*

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BIOLOGIC falsely positive reactions for syphilis in all reports to date have been recognized predominantly in young adults. They are more subject to routine testing for syphilis because of entry into the Armed Forces, marriage, or employment. This fact may be responsible for the recognition of the biologic falsely positive reaction at this time of life. To ascertain if this reaction might begin even earlier than we are accustomed to expect, we analyzed our entire series to determine the known age of the recognition of the reaction. We found that in our total series, the reaction was known to have been present in 20 per cent before the age of 18.[1]

Our interest was also stimulated by finding in several children a recurrence of a positive serologic test for syphilis (STS) with a negative *Treponema pallidum* immobilization test (TPI) after the positive findings evidencing passive transfer of the STS and/or the TPI had become negative. These children had all been born of mothers treated for syphilis. It was by mere chance that they were again tested, as it had been thought that they would remain negative after the temporary positive reactions from passive transfer of antibody had disappeared. This study was undertaken to ascertain if this pattern occurred in any significant number of instances.

Our material came entirely from our clinic at the Columbia Presbyterian Medical Center to which are referred all babies born of mothers showing any deviation in serologic tests for syphilis.

This study is based on data from 400 children (Table I). They have been divided into 4 major groups depending upon the status of the mother in relation to syphilis, upon tests for it at the time of the baby's birth, or upon a falsely positive test in the child. The largest group consisted of children born of mothers treated for syphilis whose offspring were carefully studied because of the history of syphilis or of pe-

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sistently positive STS in the mother. The second largest group was composed of children born of mothers with biologic falsely positive reactions. Some of these mothers had been treated for syphilis as a precautionary measure but many had received no treatment; none of their infants had congenital syphilis. The third group was composed of children in our Dermatology Clinic who had positive reactions on routine serologic testing for syphilis. The mothers were then studied and found to have negative reactions to these tests. The fourth group is of particular interest. The mothers had active syphilis which had not been recognized before the birth of the baby, and they had received no treatment for it.

Two hundred and sixty-three infants were studied within the period after birth necessary to demonstrate passive transfer. As shown in a previous report,[2] evidence of passive transfer of antibodies for syphilis as demonstrated by serologic tests usually disappears within 3 months after birth and that measured by the *Treponema pallidum* immobilization test disappears within 6 months. No infant was considered to be a biologic falsely positive reactor unless all tests for syphilis had reverted to complete negativity, when evidence of passive transfer had been present, and who subsequently developed positive serologic tests while the TPI test remained negative. The remaining 137 children were first seen after the age of 3 months, and for that reason the presence or absence of passive transfer is unknown.

In adults the preponderance of females over males with biologic falsely positive reactions has been evident in all studies. In our series of adults,[3] 71 per cent were females and 29 per cent were males. In a previous study,[1] we found that the proportion between the sexes in children 10 to 18 years of age was approximately the same as in adults. In children under 10 years of age, however, the proportion of females was only 58 per cent. In the present series of infants and very young children, 55 per cent were females and 45 per cent were males.

In Table II it will be noted that no infant born to a mother treated for syphilis had evidence of congenital syphilis. It is of interest to note that of 221 children born of mothers treated for syphilis, 66 per cent had passive transfer of STS and/or TPI antibody. Of the 145 infants who had evidence of passive transfer, 6.9 per cent subsequently developed a biologic falsely positive reaction. Of 84 children whose status regarding passive transfer was unknown, 8.3 per cent had a biologic falsely positive reaction.

Of 73 infants born of mothers known to have a biologic falsely positive reaction, 13 (17.8 per cent) of the infants developed a similar reaction (Table III). It should be especially noted that, although the numbers are small, no baby who developed a biologic

**Table I.** Classification of 400 children as biologic falsely positive reactors, syphilitic, or nonsyphilitic according to the syphilitic status of the mother

| *Status of mothers* | *Total No. of children* | *Status of children* | | |
|---|---|---|---|---|
| | | *Biologic falsely positive* | *Normal* | *Syphilitic* |
| Treated syphilitic patients | 305 | 25 | 280 | 0 |
| Biologic falsely positive reactors | 73 | 13 | 60 | 0 |
| STS* and TPI† negative | 18 | 7 | 11 | 0 |
| Active syphilitic patients | 4 | 0 | 0 | 4 |
| Total | 400 | 45 | 351 | 4 |

*STS = Serologic test for syphilis.
†TPI = *Treponema pallidum* immobilization test.

**Table II.** Data of 305 infants of treated syphilitic mothers

| *Group* | *Number* |
|---|---|
| Congenital syphilitic patients | 0 |
| Passive antibody transfer with reversal to negativity | 135 |
| Passive antibody transfer with reversal to negativity and later biologic falsely positive reactions | 10 |
| No passive antibody transfer with STS* negativity | 68 |
| No passive antibody transfer with later biologic falsely positive activity | 8 |
| Status of passive transfer unknown (no biologic falsely positive reaction) | 77 |
| Status of passive transfer unknown (biologic falsely positive reaction) | 7 |
| Total | 305 |

*STS = Serologic test for syphilis.

**Table III.** Incidence of biologic falsely positive reactions in babies of biologic falsely positive mothers

| *Biologic falsely positive status of mothers* | *Status of babies* | | |
|---|---|---|---|
| | *Biologic falsely positive reactors* | *No evidence of biologic falsely positive* | *Total* |
| *Persistent* | 9 | 40 | 49 |
| *Temporary* | 0 | 8 | 8 |
| *Duration unknown* | 4 | 12 | 16 |
| Total | 13 | 60 | 73 |

**Table IV.** Distribution of STS* patterns in children with biologic falsely positive reactions

| *STS patterns* | | | |
|---|---|---|---|
| *Mazzini* | *VDRL* | *Kolmer's* | *Number* |
| Positive | Positive | Positive | 6 |
| Positive | Negative | Positive | 2 |
| Positive | Positive | Negative | 1 |
| Positive | Negative | Negative | 31 |
| Negative | Positive | Negative | 1 |
| Negative | Negative | Positive | 4 |
| Total | | | 45 |

*STS = Serologic test for syphilis.

falsely positive reaction was born of a mother with a temporary biologic falsely positive reaction. The following data concerning the children of mothers who were biologic falsely positive reactors are not shown in Table III: 42 of the 73 children were seen early enough to demonstrate passive transfer of STS antibody and 2 (5 per cent) of them had passive transfer of the STS antibody. TPI tests were done routinely and all were negative.

The distribution of the pattern of the serologic tests for syphilis is given in Table IV. In the majority of infants, the Mazzini was the only test which produced a positive result. As we have stated at other times, there may be many who will criticize our interpretation that a patient with only a reactive Mazzini is considered to be a biologic falsely positive reactor. In 1,300 specimens with positive TPI tests, however, the Mazzini test was negative in only 5 per cent, whereas the Kolmer's and the VDRL tests were negative in 20 per cent. In 64 adults with treated congenital syphilis, the Mazzini test was the only one positive in 10 per cent. On the basis of this and other evidence, we feel we cannot consider that a positive Mazzini test has no significance.

## COMMENT

The importance of the biologic falsely positive reaction in adults is now appreciated by the majority of the medical profession. Approximately 40 per cent of adults with positive serologic tests have been proven to be biologic falsely positive reactors on the basis of negative results to specific treponemal tests. Several studies by different groups[3, 4] have indicated that the biologic falsely positive reaction may be a warning, often the first, of serious import for the patient. We found in a previous study[1] that 10 per cent of our group of biologic fasely positive reactors under 8 years of age had evidence of a systemic disease. The incidence of systemic lupus erythematosus was 2 per cent, as it was in our adult group.

The group reported here are predominantly infants and very young children. A few older children have been included as they were siblings of the infants in the study group. The incidence of systemic disease in this very young age group has been much lower than that among the older children; this is not unexpected.

The high incidence (66 per cent) of passive transfer of STS and/or TPI antibodies in babies born of syphilitic mothers should be stressed, since no antisyphilitic treatment is indicated. This feature is of particular importance where an adequately treated syphilitic mother is permitted to go through a second pregnancy without treatment. There is a good chance (66 per cent in this series) of passive transfer of STS and/or TPI antibodies. It is interesting that only 2 (5 per cent) infants born of mothers with biologic falsely positive reactions had passive transfer of the STS antibody. Passive transfer, when present in 1 child, may or may not be demonstrable in a second child of the same mother. It is of probable importance that in only 2 (5 per cent) of the infants born of mothers with biologic falsely positive reactions was passive transfer demonstrated. This 5 per cent of passive transfer contrasts sharply with the 66 per cent noted in infants born of treated syphilitic mothers.

In this study we found that 8.3 per cent of infants born of treated syphilitic mothers and 18 per cent of infants born of mothers with biologic falsely positive reactions were biologic falsely positive reactors. The higher percentage of infants with biologic falsely positive reactions born of mothers with this reaction, in contrast to those with such reactions born of syphilitic mothers, may be of some significance as yet not understood. Perhaps, this difference in incidence may be due to the fact that of 13 children with the biologic falsely positive reaction, born of mothers with this reaction, 4 and 2, respectively, were siblings. Of the remaining 7 children, 2 had brothers or sisters with negative findings.

Among the 25 children with biologic falsely positive reactions, born of mothers treated for syphilis, 22 were the only children with this reaction, although 15 of them had siblings with negative tests. Three children of one mother in this group had a falsely positive reaction. The significance of the occurrence of the biologic falsely positive reaction in all children of certain families is not understood.

The family with 4 children, all of whom were biologic falsely positive reactors, was thoroughly studied. The father had positive STS and TPI tests and had never received syphilitic therapy. The mother has been a biologic falsely positive reactor for the 4 years we have studied her. The children, ranging from 10 to 15 years of age, all have persistently positive false reactions. Tests including sedimentation rates, cephalin flocculation, thymol turbidity, and electrophoretic patterns of serum proteins were done on all members of this family. The mother and all 4 children had positive thymol turbidity and cephalin flocculation tests and a diffuse elevation of the gamma globulin; the last was only slightly elevated in the children. The mother also had an increased sedimentation rate. All of these tests on the father were within normal limits.

In two instances, children, whose respective mothers had been treated for congenital syphilis and who had no stigmas, had negative serologic tests. The grandmother in each instance was found to react positively to STS and to the TPI. The mother of one of these children has developed systemic lupus erythematosus, and the other one has had chorea and rheumatic heart disease. It is difficult to classify these mothers with certainty as we have a number of instances where the TPI test has become negative with the passage of time in patients treated for congenital syphilis.

In our experience there is a tendency for the biologic falsely positive reaction in children to vary from time to time. We have the impression that during intercurrent disease this reaction may become more pronounced.

## SUMMARY

1. An incidence of 11 per cent of biologic falsely positive reactors has been observed in a series of 400 selected infants and young children.

2. Passive transfer was noted in 66 per cent of infants born of mothers treated for syphilis and in only 5 per cent of infants born of mothers with the biologic falsely positive reaction. No antisyphilitic treatment should be given to these infants.

3. Eighteen per cent of infants born of mothers with biologic falsely positive reactions developed a similar reaction; whereas only 8 per cent of infants born of mothers treated for syphilis had this reaction.

4. The incidence of systemic disease associated with biologic falsely positive reactions was not high, probably because of the very young age of the patients.


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# Recent increase in mortality from hyaline membrane disease

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EXTENSIVE atelectasis with hyaline membranes remains one of the most frequent findings at postmortem examination of liveborn premature infants. Recent studies have emphasized the role of prematurity in the pathogenesis of this condition.[1, 2] If the disease is a consequence of immaturity of the lung with respect to its protein composition, as these reports suggest, then it would be expected that it would be more common the more premature the infant.[3, 4] It is also probable that the risk of getting the disease would be the same from decade to decade and, since there is no definitive treatment for the condition, the risk of dying from the disease should also be the same. If the condition is aggravated or alleviated by any change in environment, as for example the therapeutic regimen, this might become evident in comparison of the "incidence" of fatal disease, defined as numbers dying with the disease divided by numbers born.

The roles of maternal complications and of asphyxia of the newborn infant in the pathogenesis of the disease have been examined by James.[5] His findings of a good correlation between difficulty in the initiation of breathing and subsequent clinical respiratory distress are suggestive that asphyxia and its biochemical sequelae at least increase the tendency to the disease. Others have suggested that the high oxygen concentration in the inspired air might be detrimental or even cause the condition.[6-9] Here then are two conflicting points of view.

This study was undertaken to compare two 5 years periods, 1944-1948, and 1954-1958, with respect to the "incidence" of fatal hyaline membrane disease, and the weight distribution of the affected infants born in The Johns Hopkins Hospital. In the periods chosen, the use of oxygen in infant incubators underwent a significant change. In 1944-1948, higher concentrations were employed than in 1954-1958. This was because the role of oxygen in the pathogenesis of retrolental fibroplasia was defined in the interval, and pediatricians became reluctant to raise the oxygen concentration in incubators to more than 40 per cent.[10, 11] In both eras, oxygen was fre-

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quently used in the delivery room. Generally infants were placed in an incubator at 30 minutes to 1 hour after the time of delivery. In the 1944-1948 group, the oxygen concentration was not measured, but for any infant with respiratory difficulty, and indeed for nearly all premature infants, oxygen was administered at a rate sufficient to give an environmental level of 60 to 80 per cent. The best evidence for this is the high incidence of retrolental fibroplasia in the nursery during this period.[12] This was the most striking and consistent change in the management of premature infants; clearly other modifications were introduced and these are not controlled in the present study. Very little analgesia or anesthesia was given to the mothers since it was clear that they were in premature labor. No attempt was made in this retrospective study to compare the clinical estimates of the condition of the infants at birth or to assess the incidence of respiratory distress (Table I).

## METHODS

Included in this analysis were all liveborn infants surviving more than 30 minutes and less than 6 days, born at The Johns Hopkins Hospital with a birth weight of less than 2,500 grams, subjected to autopsy in the period April 15, 1944, to April 15, 1949 (Group I), and Sept. 1, 1954, to Sept. 1, 1959 (Group II). The clinical histories were reviewed to be certain of birth weight, place of birth, and duration of life. The histologic sections of lungs from these cases were reviewed by a single observer. The diagnosis of hyaline membrane disease was based on the presence of homogeneous acellular eosinophilic material lining air spaces, alveolar ducts, and bronchioles, associated with atelectasis of the intervening parenchyma. The presence of a frothy protein coagulum, occasional polymorphonuclear leukocytes, a small hemorrhagic focus, or small remnants of aspirated vernix in the alveoli did not preclude the diagnosis. However, if material suggesting "membrane" was seen only sparsely in the presence of extensive atelectasis, massive aspiration of amniotic debris, pneumonia, or hemorrhage, the lung was classified according to the predominant lesion rather than as showing hyaline membrane disease.

The number of liveborn infants delivered at The Johns Hopkins Hospital from Jan. 1, 1944, to Dec. 3, 1948, and Jan. 1, 1954, to Dec. 30, 1958, was taken from the annual reports of the Department of Obstetrics.* The weight groups were tabulated separately. The method of recording changed slightly in this period, with the lower weight limit as 800 grams in the early period and 400 grams in the recent period. These differences are noted on Tables II and III. The two groups of infants are compared with respect to race distribution, stillbirth to live birth ratio, incidence of Cesarean section, and maternal diabetes in Table I.

## RESULTS

It is clear that there was no reduction in the "incidence" of hyaline membrane disease with the advent of lower oxygen concentrations in infant incubators. Actually the occurrence of the disease appears to be higher in the more recent period of study. For liveborn premature infants over 1,000 grams birth weight, in 1944-1948, 1.5 per cent of all infants had the lesion at autopsy, compared to 3.8 per cent in the more recent period.

The infants weighing less than 1,000 grams at birth are of special interest in that, if the disease were primarily related to immaturity of the lung, then its "incidence" should be highest in this group. In Table II (1944-1948) it is apparent that in 17 autopsies of infants weighing 400-799 grams there was no instance of hyaline membrane disease and there were only 3 cases in 18 autopsies of infants weighing

*The numbers of premature infants autopsied were determined from the files of the Department of Pathology and the numbers born from the obstetrical index. The intervals are of identical length. The actual time is shifted 4 months in the first group, and 9 months in the second because of coding differences. Since the birth and death rates change so little in the short periods, this discrepancy does not alter the results.

**Table IA.** Comparison of groups of infants weighing more than 1,000 grams (from obstetrical index)

| Birth weight | Group I (1944-1948) | | | | | | Group II (1954-1958) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | White | | | Negro | | | White | | | Negro | | |
| | Births | Deaths | | Births | Deaths | | Births | Deaths | | Births | Deaths | |
| | | No. | % | | No. | % | | No. | % | | No. | % |
| 1,000-1,499 | 38 | 14 | 36.8 | 55 | 25 | 45.0 | 44 | 25 | 56.8 | 108 | 63 | 58.3 |
| 1,500-1,999 | 86 | 8 | 9.3 | 124 | 21 | 16.9 | 117 | 26 | 22.2 | 190 | 31 | 16.3 |
| 2,000-2,499 | 355 | 11 | 3.1 | 494 | 16 | 3.2 | 379 | 22 | 5.8 | 654 | 19 | 2.9 |
| Total | 479 | 33 | 6.9 | 673 | 62 | 9.2 | 540 | 73 | 13.5 | 952 | 113 | 11.9 |

**Table IB.** Race distribution of infants autopsied (from pathology files)

| | Group I (1944-1948) | | | Group II (1954-1958) | | |
|---|---|---|---|---|---|---|
| | Total | Hyaline membrane | | Total | Hyaline membrane | |
| | | No. | % | | No. | % |
| White | 37 | 7 | 18.9 | 44 | 22 | 50.0 |
| Negro | 33 | 10 | 30.3 | 101 | 34 | 33.6 |

**Table IC.** Other factors

| | Sample year | |
|---|---|---|
| | 1947 | 1957 |
| Stillbirths | 59 (23.2/1,000 births) | 70 (20.4/1,000 births) |
| Cesarean section | 118 (4.7% deliveries) | 167 (4.9% deliveries) |
| Maternal diabetes | 18 (0.72% deliveries) | 23 (0.68% deliveries) |

800-999 grams. In Table III (1954-1958) for the group weighing 400-799 grams there were only 5 cases of hyaline membrane disease in 68 autopsies, and in the 800-999 grams group, 4 cases in 42 autopsies. In each decade, the "incidence" is highest among the infants of 1,000-1,499 grams birth weight. One obvious possibility to explain this apparent difference is that very immature infants survive for such a short time that the full histologic picture of the disease does not develop. Hyaline membranes do not occur in stillborn infants and are rare in any child who dies within 2 hours after delivery. The duration of life of all infants with birth weights under 999 grams is plotted against birth weight in Figs. 1 and 2. It is at once apparent that many died within a few hours; probably the lungs were never ventilated well, and the infants were not then "at risk" from a disease which is seen only after the lungs have been ventilated. It is also clear, however, that a large number who survived for more than 24 hours did not have hyaline membranes at autopsy. If these infants who survived less than 4 hours are eliminated from consideration, the 1944-1948 "incidence" in the 800-999 grams group is unchanged; 3 per 18 autopsies or 16 per cent. In 1954-1958 the "incidence" in the 800-999 grams group is 9.5 per cent, still much lower than the figure for the 1,000-1,499 grams babies. The percentage of autopsies

Fig. 1.

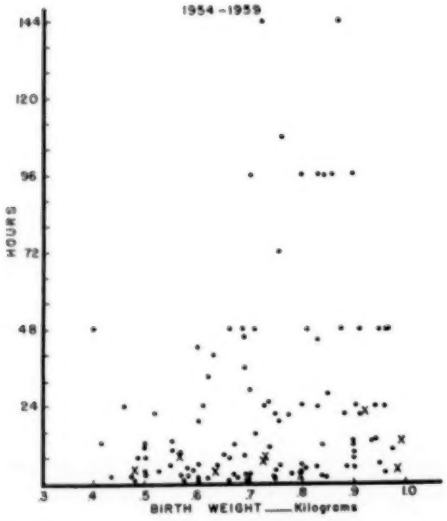


Fig. 2.

**Figs. 1 and 2.** Birth weight in kilograms is plotted against duration of life for all liveborn infants under 1 Kg.

X = hyaline membranes with atelectasis

• = no hyaline membranes.

in the total infant population was over 80 per cent in each period of study.

It may be that the rarity of the lesion in very immature lungs is related to structure alone. When the air spaces are still lined by cuboidal epithelium, and the capillaries widely separated from them, the lung is known to be less distensible than it is later in gestation,[13] and conceivably it might be less susceptible to vascular engorgement and transudation.

The marked reduction in fatal hyaline membrane disease with each 500 gram increase in birth weight over 1,000 grams underscores the association of prematurity and disease. This could be taken to support the concept of immaturity of the lung contributing to the "incidence" of fatal disease if the anatomic explanation for the failure to see the lesion frequently in infants under 1,000 grams is correct.

The duration of life of the infants with hyaline membrane disease in this study was more than 30 minutes and less than 6 days. Figs. 3 and 4 illustrate the scatter and also show that birth weight and length of survival were unrelated, a somewhat unexpected finding.

The autopsy incidence of hyaline membrane disease was also determined using all the material available on infants weighing up to 2,500 grams, including sections from lungs of those born elsewhere who died in The Johns Hopkins Hospital. In 1944-1948, among 265 autopsies, there were 58 cases of hyaline membrane disease (21.9 per cent), and in 1954-1958, in 366 autopsies there were 96 cases (26.2 per cent). Thus these figures as well show an apparent upward trend in deaths with hyaline membrane disease in recent years.

## DISCUSSION

In a previous study from this hospital, covering the years 1937 to 1949, Latham, Nesbitt, and Anderson[14] reported that of 313 neonatal deaths in the weight groups 1,000-2,499 grams, there were 257 autopsies (82 per cent) of which 98 (31 per cent) revealed hyaline membrane disease. Appy-

ing the same formula used by Latham and co-workers (cases of hyaline membrane disease over neonatal deaths), calculation for 1944-1948 using the present data gives a result of only 17/95 = 17.9 per cent. This apparent discrepancy may be attributable to a difference in diagnostic criteria employed. Widespread atelectasis with membranes being only rarely demonstrated, Latham's "grade I," may well represent the same pathologic process, but, as mentioned previously, such cases were not classified as hyaline membrane disease in the present study. It is not our intent to standardize nomenclature, or to establish criteria for histologic diagnosis. However, by having the same pathologist review *all* microscopic sections, it is likely that *consistency* in diagnosis has been achieved. This difference in the reported incidence of a disease from a single hospital, however, well illustrates the difficulty of comparing data collected by many observers, and of attempting to ascertain the "incidence" of this or any other disease in different institutions or countries.

The 2 groups compared in the present study differ not only in the "incidence" of hyaline membrane disease, but also in overall mortality. For the infants over 1,000 grams and under 2,500 grams, the mortality rate in 1944-1948 was 8.2 per cent, and in 1954-1958 it was 12.5 per cent. Table I shows that the increase cannot be attributed to the change in the proportion of Negro to white patients. It is also apparent that

**Table II.** Group I—1944-1948

| *Birth weight (Grams)* | *Births* | *Deaths* | *% deaths* | *Autopsies* reviewed* | *Hyaline membrane disease* | $\frac{HMD}{Births} \times 100$ | $\frac{HMD}{Autopsies} \times 100$ |
|---|---|---|---|---|---|---|---|
| 400 799 | inadequate information available | | | 17 | 0 | | (0.) |
| 800 999 | | | | 18 | 3 | | (16.6) |
| 1,000 1,499 | 93 | 39 | 42.0 | 29 | 8 | 8.6 | 27.6 |
| 1,500 1,999 | 210 | 29 | 13.0 | 24 | 6 | 2.9 | 25.0 |
| 2,000 2,499 | 849 | 27 | 3.2 | 17 | 3 | 0.3 | 17.6 |
| Total (for weights more than 1,000 grams and less than 2,499 grams) | 1,152 | 95 | 8.2 | 70 | 17 | 1.5 | 24.3 |

*Autopsies reviewed include only those of infants who lived more than 30 minutes and less than 6 days.

**Table III.** Group II—1954-1958

| *Birth weight (Grams)* | *Births* | *Deaths* | *% deaths* | *Autopsies reviewed* | *Hyaline membrane disease* | $\frac{HMD}{Births} \times 100$ | $\frac{HMD}{Autopsies} \times 100$ |
|---|---|---|---|---|---|---|---|
| 400 799 | 176 | 167 | 95 | 68 | 5 | | 7.3 |
| 800 999 | | | | 42 | 4 | | 9.5 |
| 1,000 1,499 | 152 | 88 | 58 | 74 | 27 | 17.8 | 36.5 |
| 1,500 1,999 | 307 | 57 | 18 | 49 | 19 | 6.2 | 38.8 |
| 2,000 2,499 | 1,033 | 41 | 4 | 22 | 10 | 0.97 | 45.4 |
| Total (for weights more than 1,000 grams and less than 2,499 grams) | 1,492 | 186 | 12.5 | 145 | 56 | 3.8 | 38.8 |

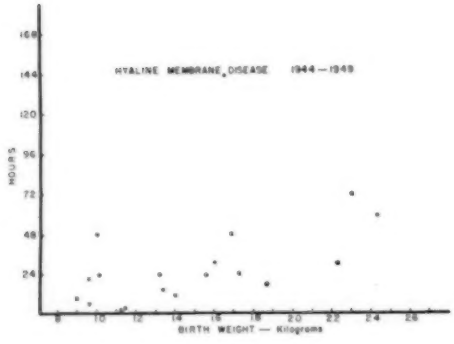


Fig. 3.

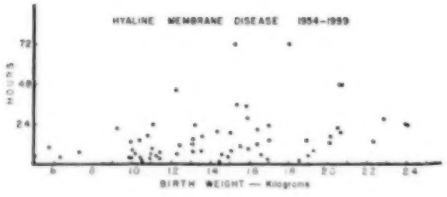


Fig. 4.

**Figs. 3 and 4.** Each dot represents an infant who showed atelectasis and hyaline membranes at autopsy. Note that the duration of life is not related to birth weight.

the change in incidence of hyaline membrane disease alone does not account for the difference. Other possible explanations for a rising mortality rate in premature infants are beyond the scope of this study.

The increase in the number of deaths from hyaline membrane disease in the period of restricted oxygen use suggests that some infants with respiratory distress may need more oxygen than they have been receiving. Certainly any danger to the infant of oxygen excess is diminished if respiratory gas exchange is seriously impaired. There must be an optimal zone of blood oxygen tension, as yet undefined in premature infants. Estimating the $pO_2$ of the blood by environmental tensions presumes normal pulmonary function; in the event of impaired function, the environmental tension may need to be much higher to sustain life.

The findings of this study pertain only to deaths from hyaline membrane disease. Its true incidence, in fact the diagnosis of it during life, cannot be determined with certainty. Therefore it is impossible to state whether the incidence has increased, or only that the case fatality rate is higher. The association of the increase in mortality with the decreased use of oxygen suggests the possibility of a causal relationship. The possibility exists that the incidence of the disease has increased, and that iatrogenic factors may play some role in its pathogenesis. This possibility is supported by the report of Hadley and associates that the disease is almost nonexistent in India.[15] This observation needs careful investigation. The findings of James[5] that neonatal asphyxia is significantly correlated with the disease make it pertinent to examine the role of analgesia and anesthesia. The present study does not throw light on this aspect of the problem.

## SUMMARY

The "incidence" of fatal hyaline membrane disease in The Johns Hopkins Hospital has been compared for two 5 year periods. During the first, 1944-1948, oxygen was widely used in the premature nursery, beginning 30 to 60 minutes after delivery. The second, 1954-1958, was an era when the concentration of oxygen in the incubators was usually restricted to below 40 per cent. A slight increase in the "incidence" of the disease in the later period makes it evident that low oxygen concentrations after the first 30 minutes were not associated with a decrease in the "incidence" of hyaline membrane disease.

The proportion of autopsies on premature infants showing hyaline membrane disease increased from 21.9 per cent in 1944-1948 to 26.2 per cent in 1954-1958.

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# *Infantile autism*

## *An analysis of 50 cases and a consideration of certain relevant neurophysiologic concepts*

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NEW HAVEN, CONN.

LEO KANNER[1] in 1943 first published his description of 11 children whose particular characteristics seemed to warrant consideration as a separate psychotic illness designated as "early infantile autism." "Two outstanding characteristics, extreme aloneness and a desire for preservation of sameness, were delineated and established as essential diagnostic criteria."[2] Onset of symptoms generally occurred during the first 2 years of life. Subsequently, Eisenberg and Kanner[3] published data on a larger series of 100 cases with information regarding their later childhood development.

Since Kanner's original report, many workers, primarily in the field of child psychiatry, have confirmed and enlarged upon the original description of these children. There has been a great deal of discussion as to the proper classification of this disorder but most workers, including Kanner, have considered this syndrome to be an extreme variant of childhood schizophrenia.[2-9] Others, however, have dissented from this viewpoint.[10-13] Van Krevelen[10] has vigorously expressed his opinion that the use of the term "schizophrenia" for autism is a misnomer. He prefers to describe this syndrome as a "retardation of the total personality development of the infant," resembling in this respect an oligophrenia rather than a schizophrenia. Van Krevelen feels that the lack of evidence of true regression of personality structure and the serious retardation of intellectual as well as affective functions are not compatible with the diagnosis of schizophrenia in these children. Much of this is essentially a semantic problem involved with the use of the term "schizophrenia." It is generally felt at present that a schizophrenic process, whatever its nature, can start in infancy and result in a lack of normal personality development rather than regression of previously established patterns.

Discussions of the etiology of autism have usually been included in the broader problem of etiology of childhood psychosis. Several excellent reviews of the widely varying concepts of psychosis in childhood have recently appeared, with particular emphases on the

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contributions of Bender, Kanner, and Mahler.[4, 15, 16] Kanner's original hypothesis was based on his observations that a high proportion of the parents of these children were of "intelligent and sophisticated stock" as compared to parents of other children in his clinic. He felt these parents were "successfully autistic" persons whose detached and emotionally sterile care of their infants was an important reason for the development of the autistic syndrome. Other workers have felt with Creak[5] that children of less socially favored families have been lost sight of as "undifferentiated mental defect." Van Krevelen[11] is diametrically opposed to Kanner's viewpoint, believing that infantile autism is the result of a profound central nervous system disturbance of unknown origin but organic in nature. Schachter is in essential agreement with Van Krevelen in this regard, referring to a specific maturational defect not ascribable to an environmental factor.[17]

Provence,[18] taking a more eclectic point of view, conceives of autistic symptomatology as a common end point resulting from various combinations of organic and environmental disturbances. She feels that the behavior disorder labeled "autism" may result from: (1) severe sensory defects such as blindness and deafness, (2) prolonged affect deprivation as in institutionalized children, (3) metabolic or structural defects of the brain particularly when associated with a poor environment, and (4) primary childhood psychosis of the autistic type. Benda and Melchior have expressed a similar point of view.[13]

Although much has appeared in the literature regarding problems of etiology, classification, and therapy in this disorder, only the Johns Hopkins group have published an analysis of the medical history, family constellation, and results of physical and laboratory examinations of a significant number of these children.[3] Essentially they found little in the way of abnormal findings other than the unusually high level of parental education previously mentioned.

The purpose of this report is to summarize and discuss our clinical findings in a group of 50 children, inmates of the Southbury Training School for mental defectives, who fulfilled criteria for the diagnosis of infantile autism as outlined below.

## DIAGNOSIS

The criteria established for inclusion in this study are as follows: (1) evidence of a severe personality disorder characterized by extreme preoccupation with self and unrelatedness to people in his environment, (2) presence of a history indicating the onset of this disorder during the first 2 years of life as manifested by the failure to develop the expected patterns of relationships to the parents or other guardians, and (3) absence of a history of serious motor retardation such as is associated with most forms of gross brain defect.

The fifty cases selected for the study do not represent all of the patients at Southbury who presented with the primary symptom of autistic behavior. Those over 18 years of age were excluded because of possible unreliability of their early developmental histories. Inadequate histories upon admission and unavailability of parents for further interrogation resulted in similar exclusions. However, it should be emphasized that if the criteria as listed above were fulfilled, the presence of other conditions as diagnosed from the past history or by physical examination did not result in the exclusion of the child from this group.

The historical data were obtained from medical and social service records. All of the children were re-examined and their cases discussed prior to inclusion in the group.

## RESULTS

Thirty-one males and 19 females were studied. This sex distribution is in contrast to the experience of Eisenberg and Kanner who found 80 males and 20 females in their 100 cases. No particular predilection toward any racial group was noted. The children averaged 7.4 years of age on admission with a range of from 3 to 13 years. Their average stay at Southbury was 3.4 years with a range of from 6 months to 10 years.

The children were all psychometrically

classified as severely retarded (low grade) although formal testing was usually impossible. Intellectual retardation and autistic personality disorder are inseparably combined in most of these children. Eisenberg[14] has given a lucid discussion of these interrelationships and we would agree with his statement that "the interdependence of emotion and intelligence is a fundamental fact of human behavior at the psychological and biologic levels of integration."

**Physical examination.** The physical and neurological examinations were all within normal limits with the exceptions of 1 child with a mild left hemiparesis, 1 child with an arrested hydrocephalus (head circumference, 54 cm.), and 2 children with severe visual defects associated with retrolental fibroplasia (both born prematurely). The head circumferences, with the one exception, were within normal limits.

Many of the children presented a superficially intelligent appearance at initial inspection, although this was variable and was not considered as a sine qua non for the diagnosis. Their behavior was characterized by a total disinterest in the examiner. Some of the children showed a short-lived but intense preoccupation with various objects in the room and would flit about erratically, examining books, ash trays, and the like. Others, however, would sit quietly in a completely withdrawn state. None of the children showed evidence of usable speech, although at times some would utter disjointed phrases devoid of communicative content. In contrast to the lack of speech and apparent unrelatedness, it was often surprising to note how much these children really understood as evidenced by their ability to follow simple directions.

**Family history.** Family histories were in agreement with the experiences of other observers in that there was a low incidence of overt mental illness in the immediate family. Three mothers and one father of the 100 parents had been diagnosed as psychotic at some time in their lives. Five sets of parents were separated or had been separated at one time. No siblings had ever been diagnosed as "autistic" and only 4 of 110 siblings had histories of any form of mental retardation, all of lesser degrees of severity as compared to the group under study.

Our impression was that the educational and socioeconomic backgrounds of the parents were similar to those of parents of other categories of severely retarded children in the institution, although we have not subjected this impression to statistical study. The parents of severely retarded children tend to have higher mean levels of educational attainment than the parents of mildly retarded children where the familial patterns of retardation are more evident. Among 47 mothers, 31 were high school graduates and 11 had attended college. Of 44 fathers, 32 were high school graduates and 16 had attended college.

**Pregnancy, perinatal, and developmental history.** Pregnancy of the mother, birth history, and neonatal course were, in general, unremarkable. The average maternal age at birth was 26.3 years, and analysis of the birth order according to the method of Penrose[19] showed this to be equivalent to that of the normal siblings. The birth dates were not concentrated in any specific month or season of the year. Five of the 50 children were premature by birth weight, although 3 of these were over 5 pounds. The 2 children with birth weights from 2 to 3 pounds had retrolental fibroplasia. One child had a definite history of brain hemorrhage during the neonatal period and 2 other children had questionable histories of neonatal distress.

Motor development as evidenced by dates of first sitting, standing, and walking alone was commonly within normal limits, although it is felt that some of these children tended to have definite motor delay as compared to a group of normal infants. Nine of the 50 children were not sitting alone by 9 months, and 12 were not walking alone by 18 months. In all of these cases except 1, the children had learned to sit by 1 year and walk by 2 years. In any event, however, motor delay never approached in severity the degree of lag in personal-social and language development.

None of these children ever developed any significant degree of usable speech. Some had histories of using words or phrases for a short period of time and then stopping and regressing in speech development. These findings would tend to support Eisenberg and Kanner's conclusion, regarding noninstitutionalized children, that failure to develop speech by 5 years of age was indicative of a poor outcome of the disease.[3]

**Onset of symptoms.** Most of the parents dated the onset of the abnormal behavior during the second year of life. The most common descriptions used were "unresponsive" and "withdrawn," failure to speak or loss of speech already required, and, at times, uncontrollable overactivity associated with the unresponsive affect. Some parents claimed to note a typical behavior during the first year of life, and in 2 cases, as young as 4 months. In these latter instances, the infant was usually described as unresponsive to the mother.

**Illnesses.** One child had pneumococcal meningitis at 3 months of age followed by what appeared to be a complete recovery. He sat at 7 months and was walking alone by 13 months. At 18 months, however, the parents first noted evidence of unresponsiveness and subsequently the characteristic picture of infantile autism became apparent.

There were no significant head injuries or major illnesses in any of the other patients (except seizures which will be described below). Encephalitis had never been diagnosed in any of these children nor were there histories of any unusual reactions to the commonly used immunization procedures.

**Seizures.** The high incidence of seizures in this group of patients came as a distinct surprise as our review of the literature dealing with autism gave no indication of such an association. Twenty-one of the 50 patients (42 per cent) had a history of one or more seizures at some time during their lives. Ten of the 21 (20 per cent) were diagnosed as epileptics on admission to Southbury. In the others, the seizures had occurred infrequently (usually less than 3 times) and this diagnosis had not been applied. Nine of the children were on anticonvulsant medication at the time of this study but none of these were having more than a rare seizure.

**Table I.** The age at onset or occurrence of seizures

| *Age at onset of seizures (years)* | *Number of cases* |
|---|---|
| 0 to 1 | 10 |
| 1 to 2 | 4 |
| 2 to 3 | 1 |
| 3 to 4 | 1 |
| 4 to 6 | 5 |
| Total | 21 or 42 per cent of 50 cases |

The types of seizures experienced by the children were quite variable. Three of the group were diagnosed as having "infantile spasms" during infancy. Others had grand mal, psychomotor, and minor motor spells or combinations of these forms. In many instances the parents dated the onset of their child's difficulties from the time of the first seizure, particularly when these occurred during the first year of life. In other cases it was clear, however, that the personality disorder antedated the first seizure.

Thus 42 per cent of our group gave evidence of having experienced one or more seizures at some time in their lives. Livingston[20] quotes Bridge as finding that 6.7 per cent of all children presenting at The Johns Hopkins Hospital or clinic had had at least one seizure during their life. Thom[21] found in a group of 3,461 normal children in Boston that 7.1 per cent had a similar history. If 7 per cent is roughly the expected incidence of seizures in a normal population of children, our figure of 42 per cent represents a highly significant increase in incidence.

**Laboratory data.** Skull x-rays were obtained on 8 children yielding no abnormalities. In 3 of the children, pneumoencephalograms carried out elsewhere were read as indicating "cerebral atrophy." Such interpretations of air studies are frequently of questionable significance. Electroencephalographic readings were available on 11 children. Six of these were interpreted as normal and 5, obtained during periods of

seizure activity, revealed diffusely abnormal tracings compatible with epileptic disorders.

Kanner mentions a total of 28 EEG studies of which 21 were read as normal, 4 equivocal, and only 3 definitely abnormal.

Other laboratory data, such as a few analyses of cerebrospinal fluid and batteries of blood chemistries, were always within normal limits.

## DISCUSSION

In considering our data, it must be remembered that these cases represent more severely affected children for whom institutionalization has become necessary. Nevertheless, most aspects of our study are in accord with previous observations about the syndrome of infantile autism. The lack of physical or neurological abnormalities, the frequency of good family backgrounds, the normal perinatal histories, and the particular pattern of onset of symptoms would all fit with the generally accepted descriptions of these children.

The high incidence of seizures in our group has heretofore not been mentioned by other observers. Kanner[2] states that only one of his 100 cases was subject to grand mal seizures. Other authors have not commented, to our knowledge, on an association between a history of seizures and the autistic syndrome. The first question to be raised is whether we are including cases in our group that others would not diagnose as infantile autism. Kanner and certain European psychiatrists have commented on the present tendency to "overuse" the diagnosis of what they consider to be an essentially rare disease. Such diagnoses as organic or chronic brain syndrome, congenital cerebral maldevelopment, epilepsy with mental retardation, and possibly others might be affixed to our cases by other observers. The presence of seizures would undoubtedly incline many workers away from the diagnosis of autism, especially where a strong bias exists in favor of an abnormal or inadequate mother-child relationship as a pathogenic explanation. In reply, we can only emphasize that we have attempted to rigorously follow the criteria set forth above, in which the common denominator, as described by Kanner, involved "the children's inability to relate themselves in the ordinary way to people and situations from almost the beginning of life." We have been unable to differentiate clinically between those of our patients with a history of seizures and those without such a history.

The high incidence of seizures in our group might conceivably be related to factors involving the admission policy at the Southbury institution. Other conditions being met, the selection of cases for admission is based primarily on the relative seriousness of the social problems and dislocations resulting from the presence of the patient in the home. The seizures in these cases were reasonably well controlled with medications and recurred so infrequently as to represent, by comparison with the behavior problem, a relatively insignificant handicap. While a selection bias on this basis may have played some role, there is little evidence to indicate this as a significant consideration.

Other reasons might be offered for the fact that workers in this field have not noted such an association. The occurrence of recurrent seizures in a child with a major personality disorder would incline the family physician toward a diagnosis of a neurological disorder and make referral to a psychiatric clinic (where the diagnosis of infantile autism is usually made) somewhat less likely. Also seizures during the early years of life that are not recurrent are generally considered as febrile convulsions and of little significance. This was the case with many of the children in our group and it was not until we determined the over-all incidence of seizures that we became aware of their unusually frequent occurrence.

The clinical data throw little light on the problem of etiology except in a negative way. There is no evidence in our histories to indicate viral encephalitides as etiological agents, although this possibility cannot be entirely excluded. The lack of histories of acute onset of the personality disorder or of any evidence of the appearance of focal neurological abnormalities would be against

encephalitis as a significant cause of this syndrome. Generalized enzymatic defects akin to phenylketonuria (to which these cases have a certain superficial resemblance) and specific defects of integrative neural mechanisms are other possibilities to be considered. We have found no indication of a familial pattern of infantile autism as might be expected with a genetically determined biochemical defect. However, a gene with varying degrees of expressivity cannot be ruled out particularly in view of Kanner's strong impression of an autistic tendency in the family of these children.

We were not able to find any significant differences in the data analyzed between those children with and those without histories of seizures. Furthermore, the total lack of correlation between the severity of the seizure pattern and the personality disorder make it unlikely that the seizure mechanism per se could be causally related to the autistic syndrome. The variegated types of seizures exhibited would be evidence against the likelihood that any single well-delineated pathologic process might be responsible for these cases.

We would feel at the present time that this tendency toward seizures is evidence of an association of cerebral abnormalities with infantile autism as defined in our criteria. This does not imply the lack of a significant effect of environmental factors in influencing the expression of this disorder. It does, however, indicate the importance of looking for abnormalities of the central nervous system in evaluating the pathogenesis of this syndrome.

Although the nature of the cerebral abnormality (or abnormalities) in autism is entirely speculative, it might be worth while to consider certain recent neurophysiologic concepts which may be germane to this problem.

**The limbic system.** Much emphasis has been placed during the past 15 years on Papez'[22] concept that the "phylogenetically old cortex and related structures provide the anatomical substratum of emotional behavior." MacLean has written extensively on this topic[23-26] and in his original paper speculated at length on the relationship of the development of affective behavior in the infant to the "phylogenetically old" brain which he later termed the *limbic system.** A great deal of experimental and clinical evidence has been developed enlarging upon this concept. It is too complex to discuss in detail here, but much of it has been recently reviewed.[26, 27] One interesting aspect of the neurophysiologic condition of the limbic system is the fact that experimental seizures are far more readily induced in this area, particularly in the hippocampal formation and amygdala, than in the neocortex.[28, 29] These seizure discharges may at times be entirely confined to the limbic system and there may be no evidence of gross motor seizures. Furthermore, it has been shown that even during seizure activity arising from deep cortical or subcortical areas, an EEG obtained with only scalp leads may not show any significant changes in resting rhythms.[30] Such observations have led MacLean to describe the dichotomy of limbic and neocortical systems as a "potential schizophysiology" of the 2 systems.[26]

Since the deficit in autistic children seems to be primarily affective in nature and in view of the susceptibility of these children to seizures as indicated in our study, one is tempted to look toward the highly excitable limbic system as a potential site of dysfunction in their central nervous systems.† This is offered as only a tentative suggestion as other subcortical structures, particularly in the central gray of the midbrain, which has extensive connections with the limbic system, may play a major role in determining be-

*Roughly equivalent to the rhinencephalon, i. e., pyriform area, cingulate gyrus (limbic lobe), hippocampal formation, fornix, amygdala, septal nuclei, and other associated nuclear structures.[24] The exact anatomic boundaries referred to by this term are not clearly definable.

†In the single autopsied case of infantile autism (with seizures) from Southbury, the only neuropathologic finding consisted of dropping out of cells in the hippocampal formation. This finding has been frequently found in patients with temporal lobe epilepsy[36] and also occurs in other cerebral illnesses. It certainly is not specific for any one disorder.

havior. Eisenberg[31] has provided an excellent discussion of the problems involved in attempting to assign a neuroanatomic locus of origin to behavior disorders. He rightly stresses the importance of regarding the normal functioning of the central nervous system as dependent upon the reciprocal interaction of the component neural systems thereby resulting in integrated behavior. However, disordered brain function in individuals with organically determined behavior disorders is likely to originate in specific neural systems, and techniques are becoming available which may allow the testing of hypotheses linking abnormal behavior to localized brain dysfunction.

On the basis of this reasoning, studies were initiated by one of us on certain aspects of 5-hydroxyindole metabolism in children diagnosed with infantile autism as compared to other retarded children. The unusually high concentrations of 5-hydroxytryptamine (serotonin) found in the limbic system[32] were one of the lines of evidence that made such an investigation seem worth while, even though such studies of schizophrenia in adults have yielded contradictory results.[33, 34] These studies will be reported in detail at a future date.[35] Our present impression is that there is no evidence of a generalized disturbance of 5-hydroxyindole metabolism in the autistic children, although certain peculiar elevations of 5-hydroxytryptamine blood levels were noted in a number of cases. However, it must be remembered that the major problem in studying neurohumoral function of the brain in humans is the difficulty in finding measurable parameters that are likely to reflect the metabolism of these substances in the brain. Sjoerdsma[34] has emphasized that it is unlikely that study of 5-hydroxytryptamine and its metabolites in blood or urine will shed much light on 5-hydroxytryptamine function in the brain. Examination of cerebrospinal fluid would seem to offer more hopeful prospects of developing significant data in this field.[37]

Although the fragmentary electroencephalographic data reported on autistic children have not been too helpful, this approach should be more intensively pursued. Surface recordings are subject to the limitations mentioned above, but direct recording from subcortical structures via stereotaxically implanted electrodes is a well-established procedure that has been performed on children.[38] These and other methods, when feasible of application, may offer considerable possibilities for investigating directly the function of subcortical structures in autistic children.

## SUMMARY AND CONCLUSIONS

1. The literature on early infantile autism has been reviewed, and the considerable differences of opinion as to the nature of this syndrome have been discussed. Our criteria for diagnosis have been set forth as primarily based on the development of a severe personality disorder during the first 2 years of life as characterized by a failure to relate to people.

2. The clinical data from 50 cases of infantile autism have been analyzed. The normal physical findings, good family backgrounds, normal perinatal histories, and particular onset of symptomatology are in general agreement with previous descriptions of this disorder.

3. Forty-two per cent of the group had histories of having had seizures at some time in their lives. Twenty per cent of the group had exhibited sufficient evidence of recurrent seizures to warrant the secondary diagnosis of "convulsive disorder" at the time of admission. This association has not been previously reported.

4. The possibility is raised that the *limbic system* is the site of a cerebral abnormality accounting for these children's susceptibility to seizures and is related to their severe affect disorder. Features of the limbic system are discussed that make it a likely locus of cerebral dysfunction in children with autistic disorders.

Dr. Gilbert Glaser provided criticism and many helpful suggestions regarding the material discussed in this paper.

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# *Homicidal deaths in infants and children*

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HOMICIDE generally is not regarded as an important cause of death in the pediatric age group. Yet 349 children under 15 years of age died in this way in 1957 in the United States and 426 more between 15 and 19 years of age were murdered.

Of special interest are the deaths during the first year of life. In 1957, the last year for which data are available, 127 infants lost their lives by homicidal violence. Forty per cent of these perished during the first day of life and more than half during the first 28 days.

In the United States infanticide is defined as slaying of the newborn infant immediately after birth, up to the moment when the birth is recorded.[1] There were 51 such deaths in 1957. Included in this category are babies found in trash cans, public toilets, parcel rooms, railway waiting rooms, and the like. Deaths for medical purposes, as in the case of craniotomy for hydrocephalus, are not included. Infanticide is classified as a form of homicide and has the same legal implications.

The most frequent method of infanticide is some variety of asphyxiation. Stab wounds through the fontanel, the heart, or the neck, and fractures of the skull, as a result of repeated blows to the head, are occasionally encountered.

The number of infanticides is probably greatly understated. Unwanted babies, many of them born out of wedlock, may be delivered into bathtubs filled with water or toilet bowls and, having no air in the lungs, are certified as stillbirths. A hand or pillow over the baby's mouth serves the same purpose. Even when homicide is suspected, the unwed mother is given the advantage of the doubt. Medical examiners are hesitant to certify a death in a baby as homicidal unless the evidence is definite, and prosecutors are disinclined to try these cases since they find themselves espousing an unpopular cause.

In 1957, 42 infants under 1 year were killed in the United States after the first month of life. This figure is also probably much below the actual number. Physicians do not often think of violence as a cause of death in babies unless the situation is brought to their attention and the physical evidence is clear-cut.

Woolley and Evans[2] have emphasized the role of parenteral violence in the production of traumatic skeletal lesions in babies. Such cases are by no means rare. Symptoms such as pain in an extremity, restricted movement of an extremity, and slight deformity are easily overlooked or disregarded especially when they are not mentioned by the parents. The bony changes are usually multiple, consisting of fractures, stripped periosteum

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**Table I.** The number of homicidal deaths in the United States, 1957*

| Age (years) | Total | White | | Non-white | |
|---|---|---|---|---|---|
| | | Male | Female | Male | Female |
| Under 1 year | 123 | 54 | 37 | 14 | 18 |
| Under 1 day | 51 | 20 | 13 | 8 | 10 |
| 1 day | 6 | 4 | 1 | 1 | 0 |
| Under 28 days | 63 | 27 | 15 | 9 | 12 |
| 1 to 4 | 88 | 23 | 31 | 18 | 16 |
| 5 to 9 | 59 | 24 | 23 | 8 | 4 |
| 10 to 14 | 79 | 31 | 17 | 24 | 7 |
| 15 to 19 | 426 | 118 | 68 | 189 | 51 |

*Source, Vital Statistics of the United States, 1957.

**Table II.** Number of homicidal deaths in England and Wales, 1957*

| Age (years) | Total | Males | Females |
|---|---|---|---|
| Under 1 year | 30 | 18 | 12 |
| 1 to 4 | 27 | 12 | 15 |
| 5 to 9 | 21 | 10 | 11 |
| 10 to 14 | 10 | 3 | 7 |
| 15 to 19 | 7 | 4 | 3 |

*Source, Registrar General's Statistical Review of England and Wales, 1957.

with subperiosteal ossification, and epiphyseal displacements. Evidence of earlier injuries is not infrequently seen in roentgenograms. A history of trauma is usually denied. Although in a certain number of these cases the lesions are produced accidentally, many are undoubtedly due to parental violence. Woolley and Evans concluded that injured children come from unstable households with a high incidence of neurotic or frankly psychotic adults.

Homicide continues to take a modest toll during childhood until the age of 15 to 19 years when a marked upswing in the number of homicides takes place (Table I).

In England and Wales the homicidal death rate is about the same as in the United States through the 5- to 9-year period after which such deaths in the United States greatly exceed those in Britain (Table II).

During the early years of life boys and girls are killed in approximately equal numbers, but after 5 to 9 years of age the number of deaths of boys exceeds that of girls. In the 15- to 19-year-old period almost twice as many white boys are murdered as girls and more than 3 times as many non-white boys as girls.

Homicide is much more frequent in non-whites than in whites. Although non-whites make up only about 11 per cent of the population, they contribute more homicidal deaths in the 15- to 19-year-old age group than the whites.

After the fourth year "assault by firearms and explosives" is the most frequent means of death, with "assault by cutting and piercing instruments" in second place. In infants and young children "assault by other means," presumably direct physical violence, is generally used.

Considerable progress has been made during the past 3 decades in reducing the mortality from homicide in children in the United States (Table III). In spite of the great increase in population (the number of births has risen from 2,203,958 in 1930 to 4,308,000 in 1957) the number of deaths has remained materially unchanged or has declined. Especially gratifying is the fall in the homicide rate in the 15- to 19-year-old age group.

**Table III.** Number of homicidal deaths in the United States by age*

| | Under 1 year | 1 to 4 | 5 to 9 | 10 to 14 | 15 to 19 |
|---|---|---|---|---|---|
| 1957 | 123 | 88 | 59 | 79 | 426 |
| 1956 | 125 | 104 | 57 | 84 | 385 |
| 1955 | 129 | 76 | 57 | 74 | 349 |
| 1954 | 134 | 90 | 57 | 93 | 400 |
| 1953 | 110 | 93 | 56 | 71 | 380 |
| 1952 | 127 | 88 | 53 | 67 | 433 |
| 1951 | 141 | 79 | 56 | 55 | 382 |
| 1950 | 137 | 74 | 65 | 68 | 417 |
| 1945 | 149 | 71 | 69 | 65 | 492 |
| 1940 | 97 | 50 | 59 | 71 | 498 |
| 1935 | 124 | 42 | 53 | 96 | 658 |
| 1930 | 131 | 76 | 91 | 111 | 721 |
| 1925 | 155 | 52 | 56 | 70 | 507 |
| 1924 | 153 | 62 | 48 | 83 | 532 |

*Source, Vital Statistics of the United States.

The physician who cares for children should be alert to the possibility of parental violence. The presence of unexplained traumatic lesions should be regarded with suspicion. The aid of social agencies should be enlisted and the family backgrounds of infants and children in whom traumatic lesions are discovered should be looked into carefully.

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# Early motor development

## Posturally induced variations

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AFTER several years' experience with the Gesell method of examination of babies in England the opportunity came to perform similar examinations on a group of babies in the United States. It was surprising to find that in their early motor behavior the American babies were more advanced in the prone position but less well developed in the supine position than would be expected of English babies. The observations on these babies are described and discussed in this report.

### MATERIALS AND METHOD

The observations were made on infants attending the Child Health Clinic at the University Hospital, Iowa City, Iowa, between December, 1958, and June, 1959. This clinic is attended by the wives of students and University personnel; all of the babies were of mixed North American stock, except for 1 Chinese baby, and all were healthy, mature infants. The infants were examined in the course of routine supervision and were not specially selected. Eighty-two infants were examined: one was seen 4 times, four were seen 3 times, and five twice. Seventy-two infants were seen only once. It would have been preferable to study more patients, and each patient more often, but this was not possible because of the clinic arrangements and the limited time available. Each mother was questioned about her child's development and her technique of baby care. The babies had complete physical and developmental examinations with particular attention being given to the early motor development in the prone and supine positions.

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### OBSERVATIONS

I shall describe first the developmental status at different age periods.

**Age 4 to 7 weeks.** There were 10 babies in the group. All 10 were very content in the prone position and made frequent attempts to raise their heads. The pelvis was flat on the couch in 8. Two babies were particularly advanced.

*Mitchell.* The development of this 4-week-old infant was recorded as follows: "The pelvis is flat on the couch. He will raise his head to a nearly vertical plane and will maintain this for several minutes. The legs and arms are moved very actively."

*James.* This 7-week-old infant was described as follows: "His pelvis is flat. He will hold his head to a nearly vertical position and will look around. Some weight is taken on his forearms and his shoulders are lifted

off the couch. For several days he has moved his position by 'scooting.' "*

In contrast to the prone position not one of the ten babies was content in the supine position for any length of time and their head control when pulled to the sitting position was just about what was expected.

**Age 8 to 11 weeks.** There were 9 babies in this group. The abilities of 4 infants when prone were not advanced but they were very assured and sustained. When they were pulled to sitting from the supine position their head control was not good but could be accepted as just reasonable for their age. Four other infants showed a much greater dissociation of behavior in the 2 positions.

*Bryan.* At 9 weeks he was "prone, he lies with the pelvis flat taking his weight on his forearms and freely raising his head. Pulled to sitting there is almost complete head lag."

*Victoria.* At 8 weeks her "weight bearing in the prone position is beginning to pass from the forearms to the hands but the arms are still flexed. She takes one arm away for moments. The pelvis is flat on the couch. She typifies the position of 'swimming' described by Gesell and Amatruda[1] and normally expected at about 16 weeks of age. When pulled to sitting and in the sitting position her head control is comparable with her age."

*Jeffrey.* At 8 weeks he was "very similar to Victoria. [He] assumes the 'swimming' position when prone. The head is fairly well fixed when pulled to the sitting position."

*Danny.* This 10-week-old boy "when prone assumes the 'swimming' position and moves his arms and legs actively. Will bear weight momentarily on one arm. 'Scoots' backwards and has been doing so for two weeks. In the supine position he seems to be interested in being raised but when this is attempted his back stiffens and he pushes bac his head. When placed sitting the head i moderately well fixed. An extension reactio is produced when he is raised from supin by a hand placed beneath his shoulders."

The 1 baby in the group unaccustomed t the prone position was quite different fro the others and more like an "average" English infant.

*Jack.* At 9 weeks, "when prone he lies still with the pelvis flat and the weight taken on his forearms. He raises his head to 45° momentarily but without sustained interest and he does not raise his shoulders off the couch. When pulled to the sitting position there is only slight head lag. He appears to appreciate this position and when sitting attempts to look about."

**Age 12 to 15 weeks.** There were 13 babies in this group and all showed a discrepancy in motor development in the prone and supine positions. Typically, in the prone position the babies were content and appeared to be willing to lie there for a long time. The pelvis was flat and the head and chest were raised high off the couch. Two had already reached the stage of bearing weight on their hands with arms extended, and two others were almost at that stage. All these infants moved their arms and legs actively and scooting was often reported and observed. One infant adopted a "flying" position and maintained it for several minutes, that is, the legs, raised as in the swimming position, and the arms, widely adducted at the shoulders, were both well off the couch.

In contrast, the babies were relatively quiet when placed in the supine position but soon became fretful. None was apparently interested in being raised to the sitting position, and when this was attempted most of them showed moderate head lag and none had good head control. Several children also showed active backward extension of the head when raised and this reaction was best demonstrated by raising the infant with a hand placed beneath the shoulders. Four children showed this response very strongly.

**Age 16 to 19 weeks.** There were 9 babies

*"Scooting" is a term in common use in America, but relatively unknown in England. It signifies the ability to move either forward or backward in the prone position by pulling and pushing with the arms and with dragging of the abdomen and legs. It differs from crawling in that it is not purposeful, the arms are not extended or used reciprocally, and there is no associated leg flexion and extension. Scooting leads into crawling and it is difficult to say when one ends and the other begins.

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in this group. The over-all picture was of advanced development when in the prone position with early pivoting. Head lag when pulled to sitting had practically disappeared in all but 2 babies who both continued to show moderate head lag and the extension reaction when pulled to sitting.

**Age 20 to 27 weeks.** The difference between motor behavior in the 2 positions was not as apparent in the 12 babies of this group as in the groups of younger infants. They were well developed and confident in the prone position. Scooting, early crawling, and pivoting were frequently observed. Two babies were drawing up their legs, raising their pelvis and abdomen, and rocking in anticipation of creeping. The extension response was not seen in any of these babies.

**Age 28 weeks and over.** There were 45 infants in this group, but it is not profitable to separate them into smaller groups. The pertinent observations are concerned with the over-all pattern of sitting and creeping development. Thirty-five babies had been used to sleeping prone and 10 supine. The dominance of prone development was seen in the babies who slept in the prone position. Thirty-two of the 35 were crawling actively and from there developed creeping before they were able to sit securely on a plane surface. The other 3 babies showed earlier adeptness at sitting possibly because of the use of training seats, but even so the ability to sit did not appear to be a necessary preliminary to crawling.

In 8 of the 10 babies who slept on their backs sitting was well established before crawling and creeping were evident, and in several sitting seemed to be a necessary step before prone ambulation developed. These babies were anxious to be mobile. They would bounce up and down or shuffle or "hitch" in the sitting position before learning to fall forward on to their hands to reach the creeping position. In these babies the positions of sitting and creeping appeared important and crawling relatively unimportant. The other 2 babies in this group showed active crawling before they were fully secure in sitting.

## DISCUSSION

The study of this small group of infants revealed 3 distinctive features. Most of them showed superior abilities in the prone position for their age. Babies 8, 10, and 12 weeks of age, for example, were taking weight on their hands with arms extended and 1 infant of 12 weeks adopted and maintained for several minutes a "flying position" with all 4 limbs in the air. The motor development in the supine position, especially the head control when pulled to a sitting position, was not advanced, and the discrepancy of the motor development in the prone and supine positions was particularly noticeable. Several babies showed active movement against the sitting position when raised from a supine position with the head being thrust backward and the back and legs extending. This reaction was observed as early as 10 weeks and as late as 19 weeks of age.

The superiority of prone motor development was related to the sleeping position of the babies. Sixty-six of the 82 mothers (80 per cent) placed their babies in the prone position to sleep, 11 placed them in the supine position, and 5 alternated between the two positions. This relationship had been suspected from random observations before the study began so the developmental examination was carried out before the sleeping position was discussed. In each case the position of sleep as prone, supine, or mixed was correctly diagnosed from the developmental examination.

Prior to this study I had not observed the extension reaction in a normal infant but had regarded it as an early sign of cerebral palsy as described by Bobath and Bobath.[2] It is probably better regarded as an indication of a preponderance of extensor tone and may be normal in infants who spend a lot of time in the prone position.

It is always necessary to consider whether the observed variations are due to a selected group, as this one was in that the babies were the offspring of professional parents. Advanced motor development has been described in Negro infants by Geber and Dean[3] but none of these babies was Negro. Illing-

worth[4] has described advanced motor development in a few white children but these were not the offspring of parents of higher than average intelligence, and, as usually accepted, there is little correlation between gross motor development and subsequent intelligence. Furthermore, in those cases of advanced development, both white and Negro, dissociation between performance in the prone and supine positions, as occurred in this study, was not described.

The question whether exercise and training influence development has been discussed extensively in the past. The different opinions are considered by McGraw[5] who resolves some of the conflicting evidence. It is accepted that there is a basic sequence of development and that abilities are not seen before the neural structures have reached the appropriate stage of maturity. The rigidity of these views is modified by the appreciation that "in the higher organism no adaptive behaviour is at its optimum from the moment of inception, [and] at the inception of cortical participation in a given activity the movements are ordinarily staccato and poorly coordinated. Further development is reflected more by increasing integration of the movements involved than by any actual changes in motor pattern." It would seem that in infants placed in the prone position the extensor phase of development is emphasized over the flexor aspect and that prone behavior is more adept and integrated than expected.

This study raises the question of the role of sitting in the developmental pattern. Sitting did not appear to be important for the development of locomotion in the babies maintained principally in the prone position. They appeared to develop sitting as a parallel to crawling and creeping. The sitting posture seems to be an important preliminary to creeping in babies who sleep in the supine position. Illingworth,[4] whose studies have been among babies who slept in the supine position, stressed the importance of sitting but also quoted an observation that suggests that sitting may not be a deeply ingrained trait. Infants in institutions may creep before they sit and require help in learning to sit. McGraw's[6] observations are again relevant: "unlike the activities of progression there is no reflex sitting posture in the behaviour of the newborn infant. This activity is of recent phylogenetic origin and probably was never organized at nuclear level."

The differences in child rearing practices in England and in the United States are reflected in the ideas of the management of children with cerebral palsy. Thus, in England where the sitting position is considered to be important, more emphasis is placed upon getting the children to a sitting position prior to locomotion. There is undoubtedly a need for the study of the influence of training on the development of normal and handicapped children.

It is a common practice in the United States to place babies in the prone position for sleep, but I cannot recall a mother in England using this position from choice. It is remarkable that this cultural difference between the two countries should be present and yet be relatively unknown.

The reasons given by the mothers for placing their babies prone were as follows, in order of frequency: "baby is more comfortable; it is safer if they vomit; they get up their wind more easily; the head is a better shape; told to do so by doctor; helps his colic; keeps the covers on better; strengthens the back; gets thumb to mouth more easily." The reasons given are interesting but it is doubtful if these arguments would stand critical scrutiny.

The few observations reported here reflect only a very small facet of the complicated picture of infant development. They emphasize the importance of constantly seeking the cause of developmental variations rather than just accepting them.

## SUMMARY

Developmental examinations carried out on 82 young babies in a clinic in the United States showed advanced motor performances in the prone position in contrast to relatively poor performance in the supine position.

These observations are described and it is suggested that the differences noted are due to the practice of placing the babies in the prone position to sleep, as was done by 80 per cent of the mothers. The significance of these observations is discussed.

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# *Reappearance of a Blalock anastomotic murmur after treatment for bacterial endocarditis*

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SINCE 1944, surgical creation of a subclavian to pulmonary artery anastomosis (Blalock operation) has been performed for tetralogy of Fallot and other cyanotic congenital heart conditions.[1] Complications of such an operation have included operative death, progressive cardiac enlargement and failure, bacterial endocarditis, and late closure of the anastomosis.[2] Loss of patency after an initial successful anastomosis usually is related to endothelization or thrombosis of the anastomotic site. A less commonly suspected cause of obstruction is bacterial endarteritis.

This report describes the loss of a "Blalock" anastomotic murmur in a 15-year-old boy 12 years after cardiovascular operation. After diagnosis and therapy of bacterial endocarditis, the anastomotic murmur again became easily audible with concomitant evidence of increased pulmonary blood flow.

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## CASE REPORT

R. F. (No. 017-24-52), a 15-year-old white boy, was noted to have a heart murmur and cyanosis at the age of 3 days. For his entire first year of life, he had numerous daily syncopal episodes and subsequently squatted after every few steps when walking began at 18 months. At age 3 years, a right subclavian-pulmonary artery anastomosis was performed with marked decrease in his cyanosis and cessation of squatting.

The boy then did well until 13 years of age when he developed progressive somnolence, headache, and convulsions. A diagnosis of a brain abscess was made and an operation performed. Recurrent symptoms 3 months later required reoperation.

For the past 2 years, cyanosis, shortness of breath, and decreased exercise tolerance have all been progressive. When the patient was seen by Dr. S. Gilbert Blount, Jr.,[3] at age 14 years 3 months, a continuous murmur was heard; consideration of further definitive operation was delayed until increased symptoms or advanced techniques made it advisable.

One week before the patient was seen, he and 5 members of his family all had respira-

tory illness diagnosed as "flu," but while the rest of the family had recovered completely, the patient continued to have intermittent chills and daily fever up to 102° F. He had been on oral penicillin, 200,000 units daily for the past 3 years and had received Chloromycetin, 250 mg. 4 times a day for a period of 3 days at the onset of his suspected "flu."

On physical examination he was deeply cyanotic and fairly well developed. The heart was not enlarged, but a forceful precordial heave suggested marked right ventricular enlargement. There was a Grade 1, vibratory systolic murmur at the upper left and right sternal borders with a single and accentuated pulmonary second sound. No continuous murmur was audible anywhere in the anterior or posterior chest. The right radial pulse was absent. The spleen tip was palpable under the left costal margin and was slightly tender. There were several petechiae in a circular area on the right chest where an electrocardiographic lead had been placed. There was marked clubbing of the digits. The remainder of the physical examination was not remarkable.

**Course.** Bacterial endocarditis was suspected and the patient was admitted to the hospital for further studies. Initial blood count revealed severe polycythemia with a hematocrit of 75 per cent. Four of 6 initial blood cultures revealed the presence of *Neisseria pharyngis*. This organism was sensitive to all tested antibiotics so therapy was begun with 8,000,000 units of penicillin daily, administered intravenously, and 5 Gm. per day of sulfadiazine administered orally.

On the third day of therapy, the patient appeared markedly improved; cyanosis was visibly less and the heart rate was slower. At that time, a Grade 1 continuous murmur in the right upper chest became audible in the supine position. On the subsequent 2 days the murmur increased to Grade 3 intensity; there were continued improvement in the patient's general condition and a decrease in cyanosis and the hematocrit. Therapy was continued for 2 weeks with 3,000,000 units of penicillin daily, administered intramuscularly, and 6 Gm. of sulfadiazine administered orally. Subsequent blood cultures were negative, and recovery from the bacterial endarteritis appeared to be complete.

**Subsequent course.** Two months later, cardiac catheterization and angiocardiography revealed complete pulmonary atresia with a large ventricular septal defect and a patent right subclavian-pulmonary artery anastomosis. Because of persistent polycythemia and disability, a left subclavian-pulmonary artery anastomosis was performed by Dr. James V. Maloney, Jr., 1 week after definitive diagnosis. The postoperative course was complicated by congestive cardiac failure, marked cardiomegaly, and a cerebrovascular accident with right hemiplegia on the morning following operation. Over the next several weeks, the patient recovered from all of these complications and is now attending school. He is able to participate in a greater number of activities and is only minimally cyanotic. Clubbing of his digits has subsided almost completely.

## DISCUSSION

Subacute bacterial endocarditis occurred as a late complication of Blalock anastomosis in 15 of 244 patients (incidence of 6 per cent) in the group recorded by White and colleagues.[2] Only one instance of endocarditis was noted in 200 cases in Campbell's series.[4] The scarcity of pertinent published reports[5-9] suggests that such infection must be rare after subclavian-pulmonary artery anastomosis.

Appearance of a new cardiac murmur is an expected event in the course of subacute bacterial endocarditis. Murmurs may be absent if the amount of vegetation is scant or in lesions confined to the atrial walls or to the pulmonary arteries.[10] Although not observed before, it can be appreciated easily that occlusion of a surgical anastomosis by bacterial vegetation might result in the disappearance of a previously present shunt murmur. Thus, disappearance of an anastomotic murmur may have the same diagnostic value in selected instances of bacterial endocarditis as the usual notation of a new murmur in this disease.

It is believed that this case represents an instance of occlusion of the first subclavian-pulmonary artery anastomosis by bacterial embolus or thrombosis. The sudden increase in cyanosis and the hematocrit and the acute exacerbation of clinical symptoms suggest that this was indeed a possibility. This was confirmed by the improvement in clinical and laboratory status after antibacterial therapy had resulted in reopening the surgical anastomotic site. Without pathologic confirmation, it is not possible to state whether a bacterial embolus had been dislodged with therapy or if ensuing reduction in size of the infected thrombus again allowed pulmonary blood flow through the surgical shunt. It has been shown that in cases of pseudotruncus arteriosus, large amounts of collateral bronchial blood flow[11] can permit life even with occlusion of a natural or surgically created patent ductus arteriosus.

A roentgenogram of the chest taken on the day following reappearance of the anastomotic murmur revealed no embolic pneumonic changes, but this does not rule out the possibility of the passage of a small sterile embolus into one of the small pulmonary arteries.

Septicemia due to *Neisseria pharyngis* is unusual, but presence of this organism in 4 of 6 cultures in combination with the clinical picture is confirmatory. The occurrence of unusual bacterial strains in patients who have been on antibiotic therapy has been described previously.[12]

## CONCLUSION

Disappearance of a subclavian-pulmonary anastomotic murmur due to bacterial endarteritis at the anastomotic site has been described. This unusual occurrence was followed by one of even greater rarity when th anastomotic murmur reappeared after treat ment of the patient with appropriate anti bacterial therapy for his localized infection

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# Vaginal ureteral ectopy

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THE TERM ureteral ectopy is used to designate an abnormal course or termination of the ureter. It is not a rare condition in children, as over 500 cases have been reported in the world's literature. Crenshaw and Buchtel[1] state that the incidence of this anomaly is 1 in 85,150 births. Kilbane,[2] Deming,[3] Burford and associates,[4] and more recently Ellerker,[5] as well as several other authors,[6-12] have extensively reviewed the literature on this subject. More than 80 per cent of these cases have been associated with a duplication anomaly of the upper urinary tract. In Ellerker's series of 493 cases, only 3 were associated with a single ectopic kidney. In females, the ectopic ureter may appear in the vaginal vestibule, the posterior urethra, vaginal vault, or on occasion may even drain into the uterine cavity. Since Dupal in 1852 reported the first case of vaginal ureteral ectopy, several case reports have appeared.

Recently we have had the opportunity of seeing 3 girls at the Children's Hospital of Michigan who had both vaginal ureteral ectopy and renal ectopy, and the similarity of their clinical findings, roentgen studies, and pathologic findings prompted this report.

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## CASE REPORTS

**Case 1.** L. L., a 5½-year-old white girl, was seen in the outpatient clinic with chief complaints of recurrent fever, loss of weight, and constant urinary dribbling. She weighed 31 pounds. On careful questioning it was apparent that she voided normally and in good quantities, but she was constantly wet despite this. Her blood pressure on admission to the hospital was 125/70 mm. Hg, and, except for constant seepage of urine from the vagina, the physical examination was within normal limits. Urinalysis was not remarkable. A cystometrogram showed normal detrusor sensation and contractile ability. There were no uninhibited contractions. An intravenous urogram showed an enlarged renal and normal ureteral outline on the left, but no renal structure was visible on the right (Fig. 1). Cystography did not reveal any reflux, and the vaginogram was normal.

Endoscopic examination revealed normal intravesical structures on the left, but the right half of the trigone was absent and the right ureteral orifice was not visualized in the bladder or urethra. Vaginal examination after the intravenous administration of indigo carmine demonstrated the appearance

**Fig. 1.** An intravenous urogram demonstrating a normal-appearing renal outline and collecting system on the left. No demonstrable renal structures on the right (Case 1).

of the blue dye at an orifice on the anterior wall of the vagina in the midline. This vaginal orifice was catheterized, radiopaque dye injected, and a film obtained with the catheter in place (Fig. 2). At laparotomy, the kidney was a small hypoplastic segment that lay over the pelvic inlet on the right, and its arterial supply arose from the right iliac artery. A nephroureterectomy was performed. The kidney measured 3.5 by 3 by 1.5 cm. in greatest dimension and weighed 7.2 grams (normal for age, 66 grams). The ureter was of normal caliber.

**Case 2.** J. B., a 5½-year-old girl, entered the hospital with complaints of constant dribbling of urine, dysuria, and perineal irritation. She, as the patient previously mentioned, had normal voiding habits, but she was constantly wet. The only abnormality seen on physical examination was very slight dripping of urine from the vagina. The blood pressure was 120/80 mm. Hg. An intravenous urogram showed hypertrophy of the left kidney, and on one film the middle third of the right ureter was seen coursing downward below the ilium. Following the intravenous administration of indigo carmine, the dye appeared promptly in the bladder but the vaginal drainage remained clear. Cystourethroscopy showed normal intravesical structures on the left, but the right half of the trigone was absent. Attempts to demonstrate and catheterize a vaginal orifice were unsuccessful. The blood urea nitrogen ranged from 11.5 mg. per cent on admission to 31.5 mg. per cent after operation, but promptly fell to normal levels. Urinalysis was negative. A laparotomy was performed, and the right kidney was ectopic and hypoplastic, lying just to the right of the aortic bifurcation. There were 3 small arteries arising from the aorta and right iliac artery. The ureter appeared to be of normal caliber and emptied into the vagina high on its anterior wall. A nephroureterectomy was done. The kidney measured 1.5 by 1 cm. in greatest dimensions, and the ureter was of normal caliber.

**Case 3.** S. K. was an 8-year-old girl who had constant dribbling of urine both day and night. She had been toilet-trained at the age of 2 years, and, like both the preceding patients, voided normally and in good quantities but was still constantly wet. Urine was seen seeping from an orifice on the anterior vaginal wall. This orifice could not be catheterized and did not excrete indigo carmine. The blood pressure was 120/90 mm. Hg. The blood urea nitrogen was 16 mg. per cent, and urinalysis was negative. Endoscopic examination showed an absence of the right half of the trigone, and the missing ureteral orifice was not seen in the bladder or the urethra. Cystography and vaginogram were normal, and the intravenous urogram showed a normal left kidney, but no opacification was seen on the right side. A laparotomy was performed, and the right kid-

ney was hypoplastic and ectopic. It lay on the right iliac artery, and its arterial supply came from 3 small branches of that vessel. A nephroureterectomy was done. The kidney measured 2.9 by 1.5 by 0.9 cm. and weighed 2.5 grams (normal weight for age, 74 grams). The ureter was of normal caliber.

## PATHOLOGIC OBSERVATIONS

The structures of the 3 kidneys were, with a variable degree of superimposed chronic inflammation, the same. All were extremely hypoplastic, and one (Case 2) was truly minute. The basic gross pattern is demonstrated in Fig. 3, which shows a hemisected kidney and the resected portion of the ureter. A peripheral shell of grossly identifiable cortex surrounded an ill-defined, fibrous medulla. Calyces and a pelvis were not seen. The ureteral lumen could be traced in retrograde fashion to the kidney, where it dwindled into the aforementioned fibrous tissue. The kidney in another (Case 2) was, as the result of severe pyelonephritis and scarring, barely recognizable, but the same structural relationships could be discerned microscopically.

**Fig. 3.** The kidney has been hemisected to show the rim of recognizable cortical tissue surrounding the fibrous medulla. The ureter and ligated arteries are at the lower pole. A small nephrogenic cyst lies separated from the main portion of the kidney in the capsular fibrous tissue at its upper pole (Case 3).

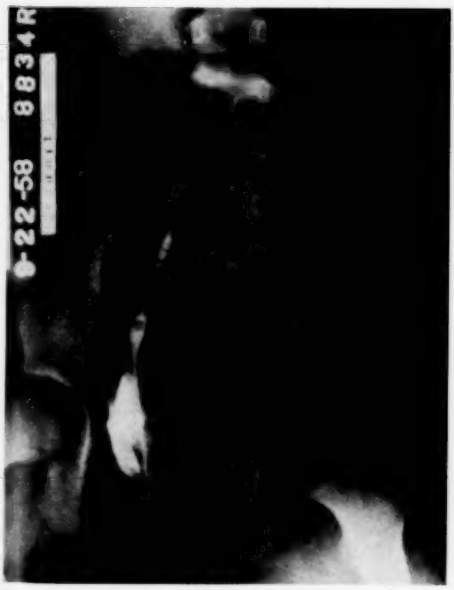


**Fig. 2.** Retrograde instillation of dye through a ureteral catheter placed in the ectopic vaginal orifice. The outline of the ectopic kidney has been superimposed in the position found at operation. The collection of dye above the pubic ramus is outside the body (Case 1).

The cortical tissue that was present was formed normally (Fig. 4), consisting of glomeruli and convoluted tubules. Small groups of collecting tubules formed narrow medullary rays, which extended into the outer medulla. It appeared as though only several segments or reniculi had formed in each kidney, and other segments may have been "aplastic" or extremely rudimentary. The cortex was, therefore, not continuous but interrupted by fibrous bands which extended from the medulla to the capsule and which contained dysplastic renal elements. Some islands of renal tissue were present outside the apparent capsules of the kidneys. Primitive tubules, scattered nephrogenic cysts, and heterotopic cartilage could be identified. The glomeruli in the areas of well-formed cortex were intrinsically normal, although there was possibly slightly more glomerulosclerosis than usual for the

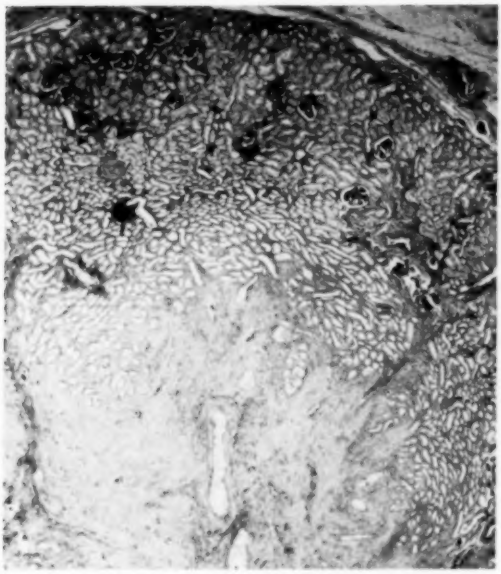

**Fig. 4.** Normally formed renal cortex. The cortex is small, but the glomeruli and convoluted tubules are normal. The medulla is markedly dysplastic (Case 1). (Periodic acid–Schiff and Alcian blue stain; × 27.)

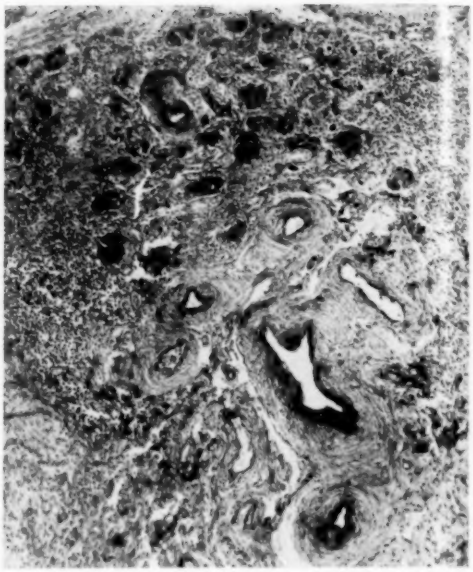

**Fig. 5.** Pyelonephritis. The attenuated cortex is scarred and infiltrated by inflammatory cells. The interlobular artery and its larger branches have thick walls because of medial hypertrophy and intimal fibrosis (Case 2). (Periodic acid–Schiff stain; × 86.)

amount of cortical tissue. Tubules were frequently slightly dilated, and occasional scars represented slightly healed tubular necrosis. Severe chronic pyelonephritis, not necessarily associated with dysplasia, was present throughout the cortex of the kidney in one (Case 2), and segmental scarring was present in another (Case 1). Severe medial hypertrophy and slight intimal fibrosis were present in 2 (Cases 1 and 2) (Fig. 5). Only negligible vascular changes were present in the other (Case 3), which suggested that the vascular changes were present in association with pyelonephritis and scarring.

The medullary tissue was, on the other hand, markedly altered (Figs. 4 and 6). It could be characterized as consisting of an abundance of stroma and a paucity of tubules. The stroma was cellular and contained a relatively large amount of smooth muscle tissue. Collecting tubules could be identified in the outer medulla, but the tubules in the inner medulla were generally primitive in type, lined by relatively undifferentiated epithelium and surrounded by lamellated fibromuscular collars. The epithelium was pseudostratified and columnar, with a variable degree of intraductal papillomatosis. These large, poorly differentiated ducts joined to form larger ducts or "calyces," which were of similar appearance. The confluence of these ducts resulted in a "pelvis" which was of the same caliber as, and continuous with, the ureter; they were lined with transitional epithelium. Collecting tubules, lined by columnar epithelium, and thin segments, corresponding to Henle's loops, were seen in only the outer medulla and were well defined in only one (Case 3). A peritubular capillary plexus was wholly lacking in the inner cortex, and the medullary tissue was poorly vascularized.

The findings were, in summary, those of severe renal hypoplasia, Some cortical se-

ments were well formed, but there was very striking medullary dysplasia and the collecting system was extremely rudimentary. Chronic pyelonephritis appeared to be a superimposed process and was associated with severe arterial sclerosis.

## DISCUSSION

A developmental basis for this form of ureteral ectopy is not well established, but two mechanisms may be postulated. The ureter normally develops as a bud from the mesonephric duct. With growth of the urogenital sinus, which receives the terminal portion of the duct, the latter is incorporated into the sinus wall. The ureter thereby gains its own orifice, which lies lateral to that of the mesonephric (Wolffian) duct. The ureteral orifice then migrates cephalad by virtue of differential growth of the sinus wall.

The most feasible explanation of the abnormality is that the ureteral orifice remains in that part of the sinus wall from which the vaginal bulb is derived, its opening then being incorporated into the vagina.[13] The explanation that has been offered more commonly is that the ureter maintains continuity with the mesonephric duct, presumably because the ureter has arisen from the duct more cephalad than customary and is not incorporated into the developing sinus wall.[14] The mesonephric duct orifice is normally located in that part of the sinus wall that differentiates into the urethra. If it remains patent, an ectopic ureteral opening may then be present in the urethra. If it does not remain patent, a fistula may develop between that part of the mesonephric duct which runs in the vaginal wall (Gartner's duct) and the vaginal lumen, producing vaginal ectopy.

The uniformity of clinical findings in this group of patients is striking. Each could have been differentiated from the common enuretic pattern by a careful history. The fact that these girls were constantly wet, yet voided in a normal fashion, is of utmost importance. They had entirely normal bladder function and sensation. Indeed, they were continent of urine, except for that portion of their urinary output which must have found egress from a point beyond that controlled by sphincter mechanisms. The combination of unilateral nonvisualization on excretory urography combined with a history of constant urinary seepage in a girl who has an otherwise normal voiding pattern would appear to be diagnostic of this condition.

A clinical observation of interest was the slight elevation of blood pressure in these patients. Arterial sclerosis, in association with chronic pyelonephritis and scarring, was present in 2 of the cases, and it is reasonable to suspect that this very slight hypertension may have been of renal origin. Following nephrectomy, the blood pressure in the other (Case 1) was 100/70 mm. Hg.

One might question the ability of these

**Fig. 6.** Medullary dysplasia. The outer medulla contains some tubules, which are separated by an excess of fibrous tissue. The inner medulla contains few tubules and blood vessels, and the dense collagenous tissue forms whorls around the ductular structures. The ductules themselves are lined by thick epithelium and have a primitive appearance (Case 1). (Periodic acid–Schiff stain; × 36.)

extremely small kidneys to produce enough urine to keep the children wet. Despite their hypoplasia, these kidneys excreted a relatively large volume of urine. It may be postulated that the normally formed cortical tissue produced a relatively normal glomerular filtrate and tubular urine and that the disparate dysplasia of the medullary tissue effected the excretion of a relatively large amount of dilute urine. Current theories of urine concentration localize the resorption of water to the medullary collecting tubules. In our cases, the medullary tissue contained so few blood vessels and normal collecting tubules that effective concentration of urine was unlikely.

## SUMMARY

In 3 children with vaginal ureteral ectopy, a uniform clinical picture of constant wetting despite normal micturition and bladder sensation was observed. Mild hypertension was present in each case. The kidneys were ectopic and hypoplastic. Although the small amount of cortical tissue that was present was normally formed, there was marked medullary dysplasia.

This anatomic pattern probably accounts for the ability of these kidneys, despite their small size, to produce sufficient urine to keep these children constantly wet.

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# Sturge-Weber syndrome; nonsurgical management

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IN 1879 Sturge[1] described a patient with a port wine mark on the right side of the head, a large right eye with vascular changes in the choroid, and left-sided convulsions, and he speculated about a vascular lesion on the surface of the right side of the brain. Weber in 1922[2] and 1929[3] and Dimitri[4] in 1923 described typical roentgenologic findings of opaque lines over the occipital and parietal regions in patients with similar clinical pictures. Since that time the classical picture of a venous angioma (port wine stain) of the face, ipsilateral intracranial calcification, contralateral paresis and atrophy, convulsions which are often contralateral and focal, and some degree of mental retardation and behavioral disorder, has been known by a variety of names, with Sturge-Weber syndrome the most widely known. The pathologic picture frequently is referred to as encephalotrigeminal angiomatosis and generally is classified with neurofibromatosis of von Recklinghausen and tuberous sclerosis as one of the neurocutaneous syndromes.

Greenwald and Koota[5] in 1936 published the first description of Sturge-Weber syndrome to appear in the American pediatric literature and reviewed the literature up to that time. The pathologic findings, pathogenesis, symptomatology, laboratory findings, and treatment of the Sturge-Weber syndrome have been thoroughly reviewed in recent excellent articles by Peterman and colleagues[6] who presented 35 cases and by Chao[7] who presented 8 cases.

It is felt that the following case represents a classical example of the Sturge-Weber syndrome and is worth reporting because of the striking intracranial calcification shown on the skull roentgenograms and because the patient's response to pediatric management has been gratifying.

## CASE REPORT

D. M., an 8-year-old Negro girl, was first seen here in January, 1958, because of generalized convulsions, weakness, and atrophy of the right arm and leg, which had been present since the age of 5 months. Apparently she had been normal prior to this time except for a port wine nevus on the left frontal area which was observed at birth. The onset of convulsions at 5 months of age led to her first hospitalization elsewhere. A diagnosis of epilepsy was made. The skull

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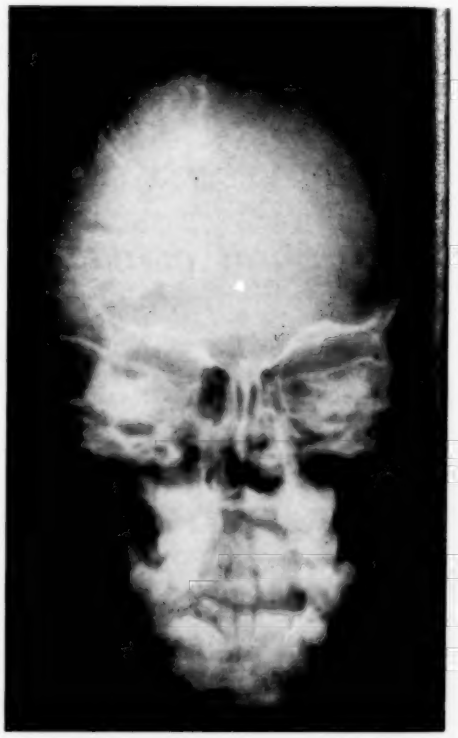
roentgenogram showed no intracranial calcification at that time. At 4 years of age she was again studied at the same hospital because of repeated convulsions and right-sided weakness and atrophy. Trephines revealed a venous angioma over the left cerebral cortex, and skull roentgenograms showed calcification over the cortex of the left occipital and parietal lobes, thus confirming the diagnosis of Sturge-Weber syndrome.

From 4 to 8 years of age the patient's convulsions were partially controlled by oral diphenylhydantoin, 50 mg. twice daily. She did not use her right arm much and the weakness of her right leg caused her to limp. According to the mother, her daughter had a poor memory, cried readily, had frequent temper tantrums and other behavior disorders, and was having great difficulty with her work in the first grade. The parents were disturbed greatly by her behavioral problems, discouraged by her school failures, and were overprotective because of the convulsions.

On physical examination she was well nourished and weighed 51½ pounds. She walked with a slight limp and there was moderate weakness and atrophy of all groups of muscle of the right arm and leg. The deep tendon reflexes were hyperactive but equal bilaterally. The port wine nevus on the left side of the face could be outlined only by close inspection. It extended over the distribution of the ophthalmic branch of the trigeminal nerve. Funduscopic and visual field examinations were within normal limits.

The roentgenograms of the skull revealed asymmetry secondary to the left hemiatrophy. Calcification was seen to follow the convolutional contours of the left occipital and parietal lobes and a portion of the temporal lobe. These calcifications were curvilinear with a double contour, delineating both sulci and gyri (Fig. 1). The hemogram and urinalysis revealed no abnormalities. The electroencephalogram, with the patient receiving phenobarbital and diphenylhydantoin, was reported as showing no seizure discharges and no focal abnormalities.

The patient has been followed in our clinic since January, 1958. Attempts to con-



*A*

*B*

**Fig. 1.** *A* and *B*, Posteroanterior and lateral skull roentgenograms of patient D. M., showing asymmetry of the skull, left hemiatrophy, and calcification over the left occipital and parietal lobes, and a portion of the temporal lobe.

trol her convulsions with diphenylhydantoin alone met with failure, since a dose of 200 mg. daily caused ataxia. In August, 1958, phenobarbital was started at 15 mg. 3 times daily and during the ensuing months the dose was gradually increased. At the present time she receives diphenylhydantoin 50 mg. 3 times daily and phenobarbital 30 mg. 4 times daily. On this schedule she only has an occasional brief seizure when she develops a fever or after a few doses of the anticonvulsant drugs have been omitted.

The nature of the disorder, the prognosis, and the treatment have been explained carefully to the parents, who have been encouraged to avoid overprotection and to permit the patient to lead as normal a life as possible. It is felt that this approach has contributed toward the decrease in her temper tantrums and other behavioral disorders. At present the patient is doing satisfactory work in the second grade.

## DISCUSSION

Dimitri[4] believed that the double contoured calcification characteristic of the Sturge-Weber syndrome was due to calcified blood vessels. In 1934 Krabbe,[8] however, showed that the shadows seen on roentgenogram actually represented calcium deposited mostly in the second and third laminae of the affected cortex. The calcium deposits characteristically occur in the parietal and occipital lobes, but they may occur, as in our case, in the temporal lobe as well. The findings are usually unilateral. It is of interest that in this case no calcification was demonstrated at 5 months of age but was marked at 4 years of age. Of the 35 cases reported by Peterman and others,[6] intracranial calcification was seen in 22 (63 per cent). The youngest patient was 4 months old; however, 6 of the 13 with normal skull films were less than 1 year old. Of Chao's[7] 8 cases, one half had typical cerebral calcification when first seen, and 2 developed calcification as they grew older.

In the management of convulsions, regardless of the cause, the anticonvulsant drug should be increased until either the convulsions are controlled or manifestations of drug toxicity appear. Frequently combinations of drugs produce better results than a single drug. Although the convulsions have been effectively controlled to date in the case reported here, it is recognized that the neurological deficits tend to progress with age so that the drugs may become less effective in the future.[7] In general, medical therapy of the Sturge-Weber syndrome is seldom satisfactory. Recently cerebral hemispherectomy has been performed on selected cases with unilateral lesions with encouraging results.[9, 10] This radical surgical approach should be reserved for those patients with contralateral weakness and atrophy who have severe and frequent convulsions which cannot be controlled by drugs.

## SUMMARY

1. A case of Sturge-Weber syndrome in an 8-year-old Negro girl is reported. The most salient feature is the skull roentgenogram which shows marked calcification in the cortex of the left occipital and parietal lobes and a portion of the temporal lobe.

2. The incidence and the location of the cerebral calcification are discussed briefly. It is emphasized that diligent efforts should be made to control the convulsions by drugs and that cerebral hemispherectomy should be considered only in those cases refractory to such therapy.

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# TROPICAL PEDIATRICS

## *Serum vitamin $B_{12}$ concentrations in kwashiorkor and marasmus*

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KWASHIORKOR is known to occur most commonly in countries where children are weaned to diets low in animal protein and presumably deficient in vitamin $B_{12}$.

It has been thought possible, therefore, that vitamin $B_{12}$ through its role in amino acid metabolism might be a factor of importance in the prevention or treatment of the condition, and that the fortification of vegetable diets with vitamin $B_{12}$ was a subject worthy of further investigation.[1]

Several trials have been undertaken to assess the growth-promoting effect of vitamin $B_{12}$ in infants and children, with conflicting results.[2-8] As Campbell and McLaughlan[9] point out, the only study to show a definite statistical effect was that of Jolliffe and associates,[10] and this was carried out in underweight children whose diet was deficient in animal protein. In none of these trials, however, was any estimation made to determine whether or not the children were deficient in vitamin $B_{12}$.

Much detailed work has been done among strict vegetarians (vegans) in Britain, America, and the Netherlands,[11, 12, 13] and it has been found that after several years some vegans develop clinical signs of vitamin $B_{12}$ deficiency and have low levels of vitamin $B_{12}$ in the serum. Children are considered to be more susceptible to the deficiency than adults, particularly in the period after weaning. This susceptibility may be due not only to increased requirements for growth but also to the lower concentrations of vitamin $B_{12}$ in the livers of infants than of adults.[14]

It is uncertain how far the results obtained in a small group of vegans can be applied to the vast numbers of vegetarians or semi-vegetarians in other parts of the world. Before exploring the possibility of fortifying vegetable foods with vitamin $B_{12}$ on a large scale, it would seem more logical to deter-

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mine first the incidence of the deficiency in countries where frank malnutrition is a serious problem, and prove more convincingly that benefit would be derived from such supplementation.

The simplest way of detecting deficiency of $B_{12}$ is by measuring the serum vitamin $B_{12}$ concentration. We have, therefore, assayed these levels in a small number of patients with kwashiorkor and marasmus, and the purpose of this paper is to report these results.

## PROCEDURE

The sera of 13 malnourished children admitted to King George VI Hospital, Nairobi, were examined and the results are recorded in Table I. The ages of the patients ranged from 1 to 6 years. Five of the children were of the marasmic type, showing marked muscle wasting, loss of subcutaneous fat, variable skin and hair changes but no edema, and 8 were of the kwashiorkor type with moderate-to-gross edema, retention of subcutaneous fat, hepatomegaly, and characteristic dermatoses.

A study of the peripheral blood and bone marrow, which will be discussed in more detail in a separate paper,[15] showed a moderate degree of anemia in both kwashiorkor and marasmus. The average hemoglobin level of the 8 patients with kwashiorkor in the present series was 9.5 Gm. per 100 ml. and that of the 5 marasmic children, 11 Gm. per 100 ml. (Table II). A mean corpuscular volume of 100 $\mu^3$ was present in one child with kwashiorkor on admission, and giant stab cells were present in the marrow in 2 cases of kwashiorkor and in 2 of marasmus. In no instance was the marrow megaloblastic. No correlation was found between the serum vitamin $B_{12}$ levels and the degree of anemia, the presence of giant stab cells in the marrow, or the finding of macrocytes in the peripheral blood. The total white cell counts in both kwashiorkor and marasmus were on an average lower than would be expected in normal children in this age group.

Follow-up estimations of the serum $B_{12}$ concentrations during recovery were made in 3 of the marasmic and 6 of the kwashiorkor group.

No supplementary vitamins were given to these children who received a diet containing approximately 44 Gm. milk protein daily. This was supplemented with sweet bananas, maize gruel, meat soup, and later minced meat and vegetables, as the appetite improved.

The serum $B_{12}$ concentrations were measured with *Euglena gracilis*.[16, 17] With this method the concentrations in normal subjects range from about 140-900 $\mu\mu$g per milliliter. Concentrations below 80 $\mu\mu$g per milliliter indicate definite $B_{12}$ deficiency while concentrations between 80 and 140 $\mu\mu$g per milliliter are of doubtful significance.

## RESULTS

The results of the serum $B_{12}$ assays are shown in Table I. In the marasmic children, the average total serum vitamin $B_{12}$ level was 341, $\mu\mu$g per milliliter with a range of 125-490 $\mu\mu$g per milliliter. In all except one patient, these results are normal, while the concentration of 125 $\mu\mu$g per milliliter is at the border line of normal. In the kwashiorkor group, the average level was 676 $\mu\mu$g per milliliter with a range of 225-1250 $\mu\mu$g per milliliter, indicating normal to high concentrations.

During recovery, the 3 marasmic children showed a rise in the serum vitamin $B_{12}$ level, whereas the levels in the kwashiorkor group tended to fall. In no serum was the free vitamin $B_{12}$ concentration more than 30 $\mu\mu$g per milliliter.

Of the 13 cases, 2 marasmic and 4 kwashiorkor patients were treated with an antibiotic (Aureomycin), but this did not appear to produce any different effect on the serum vitamin $B_{12}$ level during recovery.

## COMMENT

There appear to be very few published reports of the serum vitamin $B_{12}$ concentrations in normal children. Killander [18] found a mean concentration of 543 $\mu\mu$g per milliliter in 12 children under 1 year of age and 834 $\mu\mu$g per milliliter in 19 children

**Table I.** Total serum vitamin $B_{12}$ concentrations (micromicrogram per milliliter)*

| Case no. | Age | On admission | 2 weeks | 4 weeks | 6 weeks | 8 weeks |
|---|---|---|---|---|---|---|
| *Marasmus* | | | | | | |
| 1 | 1 year | 425† | -- | 480 | 930 | -- |
| 2 | 1 year | 300 | -- | -- | -- | 560 |
| 3 | 1 year, 6 months | 125 | 395 | -- | -- | -- |
| 4 | 6 years | 490† | -- | -- | -- | -- |
| 5 | 1 year | 365 | -- | -- | -- | -- |
| *Kwashiorkor* | | | | | | |
| 1 | 2 years, 6 months | 455† | 360 | -- | -- | -- |
| 2 | 3 years | 1,250† | 1,240 | -- | -- | -- |
| 3 | 1 year, 2 months | 255† | 155 | -- | -- | -- |
| 4 | 3 years | 640† | -- | 385 | -- | -- |
| 5 | 5 years, 6 months | 700 | 290 | -- | -- | -- |
| 6 | 3 years | 370 | -- | 235 | 360 | -- |
| 7 | 1 year | 670 | -- | -- | -- | -- |
| 8 | 5 years | 1,070 | -- | -- | -- | -- |

*The uncombined $B_{12}$ concentration was less than 30 $\mu\mu$g per milliliter in all sera.
†Patients treated with Aureomycin.

**Table II.** Hematologic estimations on admission

| | Hb. (Gm./100 ml.) | RBC (millions/ c.mm.) | PCV (%) | MCV ($\mu^3$) | MCH ($\mu\mu$g) | MCHC (%) | WBC (per c.mm.) |
|---|---|---|---|---|---|---|---|
| *Marasmus* | | | | | | | |
| 1 | 12.8 | 5.9 | 41 | 84 | 23 | 31 | 10,250 |
| 2 | 11.7 | 4.3 | 35 | 83 | 27 | 33 | 5,333 |
| 3* | 10.8 | 3.6 | 34 | 94 | 30 | 32 | 9,250 |
| 4 | 11.4 | 3.8 | 36 | 94 | 30 | 32 | 5,333 |
| 5* | 8.6 | 3.0 | 29 | 97 | 29 | 30 | 3,083 |
| *Kwashiorkor* | | | | | | | |
| 1 | 8.8 | 3.0 | 25 | 83 | 29 | 35 | 10,200 |
| 2 | 12.0 | 4.8 | 41 | 85 | 25 | 30 | 9,410 |
| 3 | 10.9 | 3.4 | 34 | 100 | 32 | 32 | 6,300 |
| 4 | 10.4 | 4.2 | 38 | 90 | 25 | 27 | 11,400 |
| 5* | 8.4 | 3.0 | 27 | 90 | 28 | 31 | 5,062 |
| 6 | 11.0 | 4.7 | 36 | 77 | 23 | 31 | 7,830 |
| 7* | 6.4 | 2.2 | 22 | 99 | 29 | 29 | 5,000 |
| 8 | 7.3 | 2.8 | 24 | 85 | 26 | 30 | 7,830 |

*Giant stab cells present in the marrow smear.

aged 1 to 9 years. In comparison with results in a series of normal European subjects,[19, 20] none of the children examined in this present study was $B_{12}$ deficient.

It should be noted, however, that serum $B_{12}$ concentrations in different racial groups of varying geographic distribution may not be identical. For example, serum $B_{12}$ levels of 160 to 2,512 $\mu\mu$g per milliliter have been reported by Davis and Pitney[21] in 140 Australian aborigines, in whom there was no apparent evidence of liver disease or abnormal hematologic picture. On the other hand, Uchino[22] has reported concentrations of 67 to 200 $\mu\mu$g per milliliter (mean 127 $\mu\mu$g per milliliter) in the sera of 22 normal Japanese adults. To what extent these differences are due to technical factors in the assay or to the nutritional state of the population is uncertain.

All the children in the present series were severely undernourished and their diet prior to admission had contained no animal protein. Although the serum $B_{12}$ concentrations were normal, it cannot be assumed that their body reserves were normal. It is only when

tissue stores are *completely* depleted of $B_{12}$ that the serum concentration falls to a very low level. Assessment of the tissue stores at present can be made only by assay of tissue concentrations, preferably the liver $B_{12}$ concentration.[23] Such estimations, however, were not practical in the present series.

Pathologic changes ranging from fatty infiltration to cirrhosis, have been described in the liver in kwashiorkor,[24-28] but less constantly in marasmus.[29] High serum vitamin $B_{12}$ levels have been recorded in various types of liver disease,[30-34] and have been related to the degree of hepatocellular damage. It is possible that the higher serum $B_{12}$ levels in the present kwashiorkor cases are an indication of the more severe liver involvement in this condition, but unfortunately no liver biopsies were done to confirm this. It is of interest that the 2 children who had total serum vitamin $B_{12}$ levels higher than 1,000 $\mu\mu$g per milliliter were the most severely ill clinically. Both had gross edema, extensive moist skin lesions and pale straight hair, and one, who had petechiae and blood blisters, subsequently died. All the vitamin $B_{12}$ was in the combined form indicating an increase in the $B_{12}$ binding capacity of the serum, such as is usually found in cases of Laennec's cirrhosis but less frequently in acute hepatitis, postnecrotic cirrhosis or hepatic coma.[32]

The fall in serum vitamin $B_{12}$ levels during recovery could be compatible with the improvement in liver pathology, or with an increased demand for available vitamin $B_{12}$ to synthesize the high protein diet given during treatment. Neither of these explanations, however, would account for the rise which occurred in the 3 cases of marasmus.

A rise in serum $B_{12}$ concentrations may be seen in patients with either $B_{12}$ or folic acid deficiency when they are treated with $B_{12}$ or folic acid,[20] so that the improved nutrition of these children in hospital may have produced this increase by repleting the tissues with $B_{12}$ and/or folic acid.

Foy and Kondi[35] have related the finding of giant stab cells in the marrow to folic acid deficiency and Walt and co-workers[36] have recommended the use of this drug in kwashiorkor in view of the high incidence of megaloblastosis in their cases.

Four children in the present series showed giant stab cells in the marrow which disappeared during dietary treatment, and this would suggest that some of these children were, in fact, folic acid deficient.

## CONCLUSION

Although it is impossible to draw firm conclusions from such a small number of cases, there was no evidence of vitamin $B_{12}$ deficiency in any of our kwashiorkor or marasmic children. The high serum $B_{12}$ concentrations found in most cases of kwashiorkor may be due to liver damage and this is supported by their tendency to fall with treatment.

The tendency of the normal serum $B_{12}$ levels in the marasmic children to rise with treatment may be due to correction of a conditioned deficiency. There seems to be sufficient difference between the 2 groups to merit more extensive investigation.

## SUMMARY

Serum $B_{12}$ estimations were made on the sera of 8 children with kwashiorkor and 5 with marasmus.

The average $B_{12}$ concentration in the kwashiorkor children was 676 $\mu\mu$g per milliliter, and in marasmic children 341 $\mu\mu$g per milliliter. No patient in either group was found to be deficient in vitamin $B_{12}$. Two of the most severely ill kwashiorkor children had concentrations of over 1,000 $\mu\mu$g per milliliter.

During the recovery, the serum $B_{12}$ concentrations fell in the kwashiorkor cases and rose in the marasmic cases. The possible significance of this finding is discussed.

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# *The serum proteins in kwashiorkor*

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KWASHIORKOR is an episode in the natural history of severe and prolonged protein deficiency in children.[1, 2, 3] A similar condition can also occur in adults.[4] Trowell[5] was the first to report that hypoproteinemia was a very constant feature of this disease. Anderson and Altman[6] reported on the electrophoretic serum protein pattern in malignant malnutrition. Using the technique of free electrophoresis in an Antweiler microelectrophoresis apparatus, they found that the outstanding features of the protein pattern are the low absolute and relative amounts of albumin compared with normal values and the high absolute and relative amounts of gamma globulin. In Kampala Thompson[7] investigated the serum protein pattern by paper electrophoresis and found a fall in the absolute and relative concentration of albumin, a marked fall in the absolute, but no change in the relative, concentration of beta globulin, and a slight fall in the absolute, but an increase in the relative, concentration of alpha globulin and of gamma globulin. Although several other reports[8-12] have since appeared, there is still lack of unanimity about the changes in the individual protein fractions, especially in the $alpha_2$, beta, and gamma globulin fractions.

This lack of agreement results partly from differences in electrophoretic technique but principally from two other considerations. The values found in kwashiorkor in African and Mexican children, on whom most of the studies have been made, are generally compared with values for healthy Europeans. It is now known that the serum protein pattern in these people differs significantly from the pattern in Europeans, especially in regard to the concentration of the gamma globulin fraction.[13-18] Moveover, because it is not always possible or convenient to obtain control samples from healthy preschool children, values for young children 1 to 3 years of age who are suffering from kwashiorkor are sometimes compared with values for healthy control children who are much older, usually with those for 5- to 10-year-olds or, in some cases, with values for adults. This introduces errors of interpretation as important changes in the serum protein pattern, particularly in the $alpha_2$, beta, and gamma globulin fractions, are now known to take place during the first 5 years of life.[19-23] For valid comparisons to be made, results in kwashiorkor must be matched within very narrow age limits with those of healthy children of the same ethnic group living in the same environment, and the studies must be made with the same technique. We have made a

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comparative study of the serum proteins of healthy Nigerian children and of kwashiorkor patients which satisfies the above criteria and the data are presented in this paper.

Total serum calcium and the calcium content of the plasma ultrafiltrate were also measured in order to determine the effect of the serum protein changes on the serum calcium.

## MATERIALS AND METHODS

**Healthy control children.** Blood was collected from approximately 450 children from 4½ months to 6½ years of age as part of a scheme to establish physiologic norms for Nigerian children. These children came from two centers: (1) Imesi, which is about 90 miles from Ibadan, and (2) Ilesha, which is between Ibadan and Imesi and 74 miles from Ibadan. The Imesi children were from 4½ months to 2½ years of age and were part of a group arising from 400 consecutive births in the village (a study of this group and their mothers has been carried out from early in the prenatal period and it is hoped that it will continue to their fifth birthdays). The Ilesha children included children from 1½ to 6½ years of age. None of the children had clinical malnutrition, but protein intake, particularly the consumption of animal proteins, may well have been below the ideal level since in the social organization of the average Nigerian family adults receive priority in the distribution of protein foods. This may be responsible for the lower albumin values found in the children as compared with those of the Nigerian adults.

**Patients with kwashiorkor.** One hundred forty-six patients with consecutive new cases of kwashiorkor who attended the pediatric clinic at University College Hospital, Ibadan, between March and December, 1958, were studied. They all showed the typical features: edema, growth retardation, wasting, and hypoproteinemia, and most of them revealed changes of the skin and hair.

**Recovered patients.** Patients who have been successfully treated with a milk diet for 30 to 120 days and who were clinically cured as judged by disappearance of edema, improvement of skin lesions, clear signs of well-being, and satisfactory gain in weight were also included in the study. Some of the patients were hospitalized, but the majority were treated as outpatients. Those treated under supervision in the hospital made more rapid recovery than those treated as outpatients. Repeat serum protein studies were made as soon as the patient was considered clinically cured according to the criteria stated above.

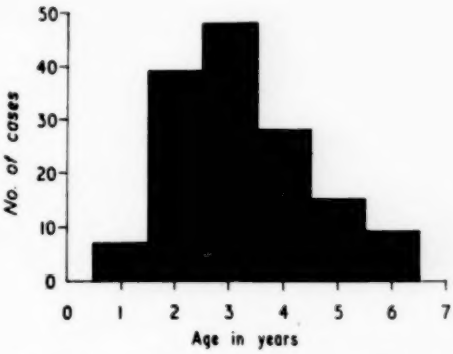


**Fig. 1.** Age distribution of 146 consecutive patients with cases of kwashiorkor seen at Ibadan, Nigeria.

Total serum protein was measured by the biuret method.[24] Paper electrophoresis was by the method of Flynn and de Mayo.[25] After drying, the papers were stained with azocarmine B and scanned with the "chromograph" or automatic reflectance densitometer.* The protein fractions were computed as percentages of the total protein by dividing the area under each peak by the total area. By applying the percentages to the total serum protein, the value of each fraction was obtained. No correction factors were applied, but the values so obtained do not differ significantly from values obtained by applying a globulin factor of 1.6 after transmission densitometry as previously described.[26]

*Produced by Joyce, Loebl and Co., Newcastle, England.

**Table I.** Mean values for total serum proteins and protein fractions in children 1 to 1½ years of age

| | *Control group (66)* | | *Kwashiorkor group (7)* | | | *Recovered group (5)* | | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Significance of difference* | *Mean* | *SD* | *Significance of difference from control* |
| *Total protein* | 6.99 | 0.60 | 3.99 | 0.35 | $P < .001$ | 6.68 | 0.46 | $.2 < P < .3$ |
| *Albumin* | 3.17 | 0.37 | 1.33 | 0.17 | $P < .001$ | 2.33 | 0.37 | $P < .001$ |
| *Alpha$_1$ globulin* | 0.34 | 0.14 | 0.26 | 0.07 | $.3 < P < .4$ | 0.40 | 0.21 | $.3 < P < .4$ |
| *Alpha$_2$ globulin* | 0.99 | 0.23 | 0.48 | 0.17 | $P < .001$ | 0.81 | 0.19 | $.05 < P < .1$ |
| *Beta globulin* | 0.97 | 0.19 | 0.34 | 0.12 | $P < .001$ | 0.80 | 0.08 | $.05 < P < .1$ |
| *Gamma globulin* | 1.52 | 0.41 | 1.58 | 0.35 | $.7 < P < .8$ | 2.34 | 0.55 | $P < .001$ |
| *Total globulin* | 3.82 | | 2.66 | | | 4.35 | | |
| *A/G ratio* | 0.83 | | 0.50 | | | 0.54 | | |

**Table II.** Mean values for total serum proteins and protein fractions in children 1½ to 2½ years of age

| | *Control group (96)* | | *Kwashiorkor group (39)* | | | *Recovered group (12)* | | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Significance of difference* | *Mean* | *SD* | *Significance of difference from control* |
| *Total protein* | 6.70 | 0.77 | 4.11 | 0.64 | $P < .001$ | 6.80 | 0.54 | $.6 < P < .7$ |
| *Albumin* | 3.00 | 0.51 | 1.27 | 0.37 | $P < .001$ | 2.77 | 0.44 | $.1 < P < .2$ |
| *Alpha$_1$ globulin* | 0.37 | 0.12 | 0.26 | 0.11 | $P < .001$ | 0.40 | 0.17 | $.4 < P < .5$ |
| *Alpha$_2$ globulin* | 0.91 | 0.19 | 0.53 | 0.24 | $P < .001$ | 0.82 | 0.20 | $.1 < P < .2$ |
| *Beta globulin* | 0.87 | 0.20 | 0.41 | 0.19 | $P < .001$ | 0.86 | 0.17 | $.8 < P < .9$ |
| *Gamma globulin* | 1.55 | 0.37 | 1.64 | 0.52 | $.2 < P < .3$ | 1.95 | 0.52 | $.001 < P < .01$ |
| *Total globulin* | 3.70 | | 2.84 | | | 4.03 | | |
| *A/G ratio* | 0.82 | | 0.45 | | | 0.69 | | |

**Table III.** Mean values for total serum proteins and protein fractions in children 2½ to 3½ years of age

| | *Control group (44)* | | *Kwashiorkor group (48)* | | | *Recovered group (12)* | | |
|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Significance of difference* | *Mean* | *SD* | *Significance of difference from control* |
| *Total protein* | 6.50 | 0.70 | 4.04 | 0.55 | $P < .001$ | 6.76 | 0.56 | $.2 < P < .3$ |
| *Albumin* | 2.79 | 0.52 | 1.24 | 0.37 | $P < .001$ | 2.64 | 0.55 | $.3 < P < .4$ |
| *Alpha$_1$ globulin* | 0.39 | 0.12 | 0.27 | 0.13 | $P < .001$ | 0.30 | 0.16 | $.02 < P < .05$ |
| *Alpha$_2$ globulin* | 0.83 | 0.17 | 0.46 | 0.17 | $P < .001$ | 0.79 | 0.28 | $.5 < P < .6$ |
| *Beta globulin* | 0.81 | 0.19 | 0.41 | 0.14 | $P < .001$ | 0.81 | 0.29 | |
| *Gamma globulin* | 1.68 | 0.35 | 1.66 | 0.52 | $.8 < P < .9$ | 2.22 | 0.69 | $P < .00$ |
| *Total globulin* | 3.71 | | 2.80 | | | 4.12 | | |
| *A/G ratio* | 0.75 | | 0.44 | | | 0.64 | | |

**Table IV.** Mean values for total serum proteins and protein fractions in children 3½ to 4½ years of age

| | *Control group (28)* | | *Kashiorkor group (28)* | | |
|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Significance of difference* |
| *Total protein* | 6.62 | 0.76 | 3.90 | 0.62 | $P < .001$ |
| *Albumin* | 2.78 | 0.49 | 1.01 | 0.41 | $P < .001$ |
| *Alpha$_1$ globulin* | 0.34 | 0.12 | 0.27 | 0.13 | $.3 < P < .4$ |
| *Alpha$_2$ globulin* | 0.81 | 0.16 | 0.51 | 0.12 | $P < .001$ |
| *Beta globulin* | 0.86 | 0.17 | 0.40 | 0.15 | $P < .001$ |
| *Gamma globulin* | 1.83 | 0.45 | 1.71 | 0.56 | $.4 < P < .5$ |
| *Total globulin* | 3.84 | | 2.89 | | |
| *A/G ratio* | 0.72 | | 0.35 | | |

**Table V.** Mean values for total serum proteins and protein fractions in children 4½ to 5½ years of age

| | *Control group (9)* | | *Kwashiorkor group (15)* | | |
|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Significance of difference* |
| *Total protein* | 6.60 | 0.56 | 3.92 | 0.48 | $P < .001$ |
| *Albumin* | 2.93 | 0.51 | 1.11 | 0.38 | $P < .001$ |
| *Alpha$_1$ globulin* | 0.34 | 0.14 | 0.30 | 0.10 | $.4 < P < .5$ |
| *Alpha$_2$ globulin* | 0.73 | 0.14 | 0.50 | 0.15 | $.001 < P < .01$ |
| *Beta globulin* | 0.77 | 0.19 | 0.38 | 0.20 | $P < .001$ |
| *Gamma globulin* | 1.83 | 0.52 | 1.63 | 0.43 | $.3 < P < .4$ |
| *Total globulin* | 3.67 | | 2.81 | | |
| *A/G ratio* | 0.80 | | 0.40 | | |

**Table VI.** Mean values for total serum proteins and protein fractions in children 5½ to 6½ years of age

| | *Control group (6)* | | *Kwashiorkor group (9)* | | |
|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Significance of difference* |
| *Total protein* | 6.43 | 0.77 | 4.10 | 0.62 | $P < .001$ |
| *Albumin* | 2.72 | 0.47 | 1.08 | 0.37 | $P < .001$ |
| *Alpha$_1$ globulin* | 0.40 | 0.14 | 0.23 | 0.13 | $.02 < P < .05$ |
| *Alpha$_2$ globulin* | 0.72 | 0.13 | 0.56 | 0.12 | $.02 < P < .05$ |
| *Beta globulin* | 0.72 | 0.11 | 0.41 | 0.18 | $.001 < P < .01$ |
| *Gamma globulin* | 1.87 | 0.53 | 1.82 | 0.70 | $.8 < P < .9$ |
| *Total globulin* | 3.71 | | 3.02 | | |
| *A/G ratio* | 0.73 | | 0.36 | | |

Total calcium in the serum and calcium in the ultrafiltrate were determined by compleximetric titration with EDTA.[27]

## RESULTS

The age distribution of the 146 patients with kwashiorkor is shown in Fig. 1. In Ibadan, kwashiorkor occurs mainly during the age of 1½ to 4½, with maximum incidence in the third year.

The mean values for total serum proteins and for the protein fractions in healthy children in patients with kwashiorkor, and in recovered patients are shown in Tables I, II, III, IV, V, and VI. A sufficient number of recovered patients older than 3½ years was not examined to allow for statistical evaluation.

Total protein is significantly reduced in patients with kwashiorkor in every age group. In recovered patients the total protein concentration has returned to normal. Albumin shows the greatest percentage reduction in every case. The albumin fraction responds promptly to treatment and, in clinically cured patients, the albumin has returned to normal in just over 50 per cent of the cases. In the remaining cases the albumin concentration is still below normal so that the mean value for the clinically cured patients is less than the normal mean value.

The mean concentration of alpha$_1$ globulin is below normal in all groups, but the difference is not statistically significant in every age period. This fraction is the most difficult to measure accurately because it is low in concentration, separation from albumin is not always very clear, and there appears to be considerable loss of protein on storage of the serum.

Alpha$_2$ globulin is reduced in every age group. The amount of change, however, varies with age, and is greatest in the younger children who normally have a high mean alpha$_2$ globulin concentration and least in the older children whose mean alpha$_2$ globulin concentration approaches the adult mean value. If the alpha$_2$ globulin figures had been compared with the adult mean concentration, the conclusion would have been drawn that there is no significant change in alpha$_2$ globulin concentration in kwashiorkor. In recovered patients the alpha$_2$ globulin concentration approaches, but has not reached, the mean value in health.

Beta globulin is also reduced in every age group to an extent almost as marked as the fall in albumin concentration. In recovered patients the beta globulin concen-

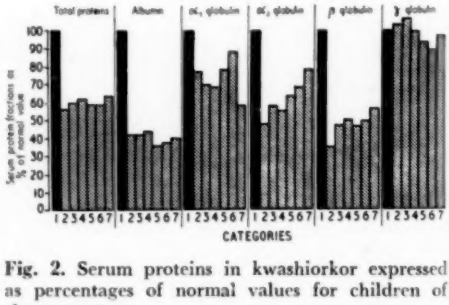


**Fig. 2.** Serum proteins in kwashiorkor expressed as percentages of normal values for children of the same age:

Group 1, normal; Group 2, kwashiorkor over 1 to 1½ years of age; Group 3, kwashiorkor over 1½ to 2½ years of age; Group 4, kwashiorkor over 2½ to 3½ years of age; Group 5, kwashiorkor over 3½ to 4½ years of age; Group 6, kwashiorkor over 4½ to 5½ years of age; and Group 7, kwashiorkor over 5½ to 6½ years of age.

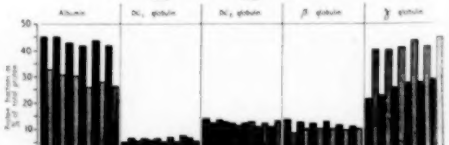


**Fig. 3.** Serum protein fractions in healthy N gerian children and in children with kwashiorko expressed as percentages of the total serum pro teins:

Group 1, kwashiorkor over 1 to 1½ years age; Group 2, kwashiorkor over 1½ to 2½ yea of age; Group 3, kwashiorkor over 2½ to 3 years of age; Group 4, kwashiorkor over 3½ t 4½ years of age; Group 5, kwashiorkor over 4 to 5½ years of age; and Group 6, kwashiorko over 5½ to 6½ years of age.

tration has not returned to the mean concentration in health.

Gamma globulin does not show significant deviation from normal. In the recovered patients there is a hypergammaglobulinemia.

The net result of these changes is that there is a greater relative fall in albumin concentration than in the total globulin concentration so that there is a reduction in the A/G ratio.

Fig. 2 shows the total serum proteins and the protein fractions in kwashiorkor expressed as percentages of the average value for children of the same age. The albumin and beta globulin fractions show greater relative change than do the other globulin fractions, and the relative fall in $alpha_2$ globulin concentration becomes less with increasing age of the patient.

Fig. 3 illustrates the changes in the serum protein fractions expressed as percentages of the total proteins. A marked fall is demonstrated in albumin, a variable change in $alpha_1$ and $alpha_2$ globulins, and a slight fall in beta globulin, while gamma globulin shows a marked increase in relative concentration.

The mean values for total calcium, and for protein-bound and ultrafiltrable calcium in healthy children and in kwashiorkor are presented in Table VII. There is a significant fall in the concentration of total calcium which is due to a decrease in the protein-bound fraction.

**Table VII.** Serum calcium in healthy children and in kwashiorkor

| | *Healthy children (19) (mg./100 ml.)* | *Kashiorkor patients (9) (mg./100 ml.)* | *P* |
|---|---|---|---|
| Total calcium | 9.7 ± 1.1 | 7.9 ± 1.2 | $P < .001$ |
| Protein-bound calcium | 5.6 ± 0.9 | 4.1 ± 0.82 | $P < .001$ |
| Ultrafiltrable calcium | 4.1 ± 0.5 | 3.8 ± 0.40 | $.1 < P < .2$ |

## DISCUSSION

Hypoproteinemia, and especially hypoalbuminemia, occurs regularly in protein deficiency states in adults as well as in children,[5-12] so that no doubt exists that the hypoproteinemia of kwashiorkor is the direct effect of the inadequate protein intake. My data confirm the finding of other workers[5-12] that the serum protein fractions are not all affected to the same degree: the albumin and beta globulin fractions are affected relatively more than the other protein fractions.

Albumin metabolism in kwashiorkor has been studied by Gitlin and others[31] using $I^{131}$-labeled albumin as a tracer. The half-life during the hypoalbuminemic period was no different from that after the albumin rose to normal during recovery, and they concluded that hypoalbuminemia is due to decreased synthesis and is unrelated to increased loss or destruction of albumin.

The liver is the principal site of the synthesis of the serum proteins with the exception of the gamma globulin fraction. In hepatic disease there is a reduction in albumin concentration and an increase in gamma globulin concentration, with net depression of the A/G ratio. It is natural therefore that attention has been chiefly focused on the liver as the probable cause of the marked depression of the A/G ratio regularly observed in kwashiorkor.

When, however patients with kwashiorkor are provided with an adequate supply of proteins, the serum albumin concentration rises very promptly,[6, 11, 32, 33] and this immediate response is evidence that the capacity of the liver for albumin synthesis had not been seriously impaired. Hyperbilirubinemia is not a frequent finding in kwashiorkor,[34, 35] and tests of liver function, including the sensitive bromsulphthalein retention test, show that less than 30 per cent of cases have evidence of severe limitation of hepatic function.[34-38] In the absence of evidence of marked depression of liver function in the majority of patients, liver damage cannot satisfactorily account for the low A/G ratio so characteristic of

the disease, although it is likely to be a factor in some cases.

Infection is a very frequent complication in kwashiorkor. The typical serum electrophoretic changes in infection consist of a moderate decrease in albumin and a slight to moderate increase in alpha$_2$ and gamma globulin.[39-42] In acute infections the alpha$_2$ globulin is mainly affected, whereas in chronic infections gamma globulin shows the greater changes. Progressively increasing hypergammaglobulinemia characterizes the recovery phase of kwashiorkor[6, 11, 43] and the serum protein pattern in patients recovered from kwashiorkor is not unlike the picture which can be produced by chronic infection. Therefore, the relative increase in serum gamma globulin in kwashiorkor may, in part, be a measure of the degree to which, as a result of infection, priority is given to the synthesis of gamma globulin in competition with all the other protein fractions for the available amino acids.

The individual serum protein fractions differ in amino acid composition. Albumin and beta globulin contain more sulfur and sulfur-containing amino acids than do alpha$_2$ and gamma globulins.[44] In kwashiorkor there is a qualitative as well as a quantitative deficiency of amino acids.[45, 46] The sulfur-containing amino acids, which are mainly supplied by the animal proteins in the diet, must be very deficient in the diet of kwashiorkor patients since the intake of animal proteins such as milk and meat is usually very severely limited. The pattern of amino acid deficiency in kwashiorkor may, therefore, play an important role in determining the serum protein spectrum as a deficiency of sulfur-containing amino acids may be one of the limiting factors in the synthesis of albumin and beta globulin. In this conection it is of interest that these 2 protein fractions are affected most severely in kwashiorkor.

Further, plasma is known to contain immune antibodies, transport proteins, and several enzymes, most of which are in the globulin fractions.[47, 48] The globulins may accordingly include proteins that physiologically are less "labile" than plasma albumin which may largely represent true "storage" protein. The synthesis of albumin may therefore be more sensitive to dietary protein intake, so that in states of protein deficiency albumin synthesis could be considerably reduced while the synthesis of most of the globulins is being maintained.

These changes in the serum proteins have important physiologic effects. One of the principal functions of the plasma proteins and in particular of the plasma albumin is the distribution of fluid within the body compartments. The studies of Peters and associates[49-53] and of Weech and Ling[54] have shown that the level of albumin in the plasma is an important factor in the genesis of clinical edema and that serum albumin values below 2.5 Gm. per 100 ml. are usually associated with edema. Edema is one of the most constant features of kwashiorkor and practically all the patients in the present study have serum albumin concentrations below 2.0 Gm. per 100 ml. The low serum albumin must, therefore, play a considerable part in the production of the edema. In the group of patients reported here, however, close correlation was not always found between the degree of edema and the concentration of total proteins or of albumin and it is clear that factors additional to the changes in plasma protein concentration must be significant when considering the etiology, the degree, and distribution of edema in kwashiorkor. Among such additional factors are alteration of renal function,[55, 56] changes in the secretion and metabolism of adrenal steroid hormones,[57] changes in the production and inactivation of posterior pituitary antidiuretic hormone[58, 59] and the release of other antidiuretic substances such as ferritin.[60]

Another function of the proteins of plasma is the transport of inorganic substances. In kwashiorkor there is a fall in the total iron binding capacity of the serum[61, 62] which is related to the decrease in beta globulin concentration. Serum copper is reduced[61, 63] and this follows closely the fall in the concentration of alpha$_2$ globulin.[62] Total serum calcium is also significantly lower than

normal[64] and our results show that this fall is due almost entirely to a reduction in the protein-bound calcium.

## SUMMARY

1. The total serum proteins and the protein fractions have been estimated in healthy Nigerian children, in children with kwashiorkor, and in patients who have recovered from kwashiorkor.

2. In kwashiorkor there is a statistically significant fall in the mean absolute concentration of total proteins, albumin, alpha$_2$ globulin, and beta globulin. Mean alpha$_1$ globulin concentration is also less than normal but the difference is not significant in all age periods. The changes in mean gamma globulin concentration are not statistically significant.

3. Albumin shows a marked fall, alpha$_1$ and alpha$_2$ globulins a variable change, and beta globulin a slight fall, while gamma globulin shows a marked rise in relative concentration.

4. It is concluded that the serum protein pattern in kwashiorkor is produced by a combination of quantitative and qualitative deficiency of amino acids, liver damage, and infection. Furthermore, the globulin fractions of the serum proteins may include proteins that are physiologically less labile than the serum albumin.

5. The changes in serum protein play an important part in the production of edema; they also account for the reduction in serum iron-binding capacity, copper, and calcium.

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# MEDICAL PROGRESS

## *The feeding of prematurely born infants—a critique of current status*

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THERE continues to be lack of agreement concerning the most nearly optimal composition of the diet for the prematurely born infant. The purpose of this paper is to present a review of certain aspects of the subject in the hope that those not working directly in this field might be better enabled to evaluate future reports and developments.

Two of the leading figures in the early history of premature care in this country were Julius Hess and Grover Powers. Dr. Hess was a firm advocate, as are many other people throughout the world, of feeding the premature infant human milk.[1] Dr. Powers' interest in this problem led him toward a different orientation. In his early observations on prematurely born infants he noted that the babies seemed to thrive more satisfactorily, as judged from their growth and freedom from digestive disturbances, on artificial milk mixtures made up to contain more protein, more carbohydrate, and less fat than human milk.[2] It is interesting that in nature the only animals which produce such high carbohydrate, high protein, and low fat milks are the horse and ass. Milk from these animals is poor in caloric content, containing a great deal of water. Ass's milk, containing only 0.45 calorie per cubic centimeter, had nevertheless been found in some countries to be of particular value in the feeding of small infants and has been advocated for the prevention of gastrointestinal disturbances.[2]

Gordon, Levine, and their associates investigated, in laboratory and controlled clinical studies, some of the concepts which had been suggested by Powers as a result of his clinical observations. They reasoned that the prematurely born infant was one in whom

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hunger and satiety could not be evaluated by the same subjective means as in his full-term counterpart and therefore by a series of very laborious and prolonged investigations attempted to determine his needs objectively. They found that when the baby received approximately 140 to 160 c.c. of water per kilogram per day he was in positive water balance. Larger volumes than this did not appear to be necessary, but merely increased the output by way of urine and stool; smaller volumes were dangerous, less than 100 c.c. per kilogram per day producing a negative water balance.[3]

The important data concerning the amount of water that should be in the diet were based on earlier studies which had indicated that the protoplasm of the premature infant was approximately 65 to 70 per cent water. When the babies studied by Gordon and Levine were fed either human milk or cow's milk formulas in the amounts of approximately 150 c.c. per kilogram per day, the babies gained about 25 grams per day on human milk, and with cow's milk almost twice as much, about 44 grams per day. However, in either case about 65 per cent of each gram of weight gained could be accounted for by retained water.[4] They therefore concluded that when approximately 150 c.c. per kilogram per day of either cow's or human milk formula was fed, the babies would gain and store water in the proportions which had previously been worked out to be associated with normal protoplasmic deposition.

In another series of experiments they showed that the babies required about 120 calories per kilogram of body weight.[5] This is based on the fact that the resting requirement, which is the closest approximation that one can make to the basal metabolism of a premature infant, added to the additional requirements imposed by physical activity, losses in the stool, and calories necessary for adequate deposition of new tissue total approximately 120 calories per kilogram. Thus, the average requirements as worked out by Levine and Gordon for the premature infant are 120 calories and 150 c.c. per kilogram of body weight in a formula containing 0.8 calorie per cubic centimeter or 24 calories per ounce. This is a fairly concentrated formula. The premature infant has difficulty with sucking and swallowing and has relatively large needs for food for growth. Thus a somewhat concentrated formula would appear to be desirable.

Other studies of Levine and Gordon were concerned with the proportions of protein, fat, and carbohydrate in the formula. From balance data, they found that within the wide limits of intakes of as little as 2.7 Gm. of protein per kilogram per day to as much as more than 9 Gm., the coefficient of digestibility or the coefficient of absorption was 90 per cent or better.[6] Reports by others have confirmed this observation.[7] As the protein content of the diet was increased Gordon and Levine found that nitrogen retention in the prematurely born infant also increased. They reasoned that the baby could store large amounts of protein and was not upset when given greater amounts of protein than were found in human milk or even in unmodified cow's milk. Full-term infants store much less on equivalent intakes. In other studies they found that the carbohydrate utilization of the premature infant as evidenced from R.Q. measurements was the same as that of the full-term, and that within wide limits of intake, most of the carbohydrate fed was utilized.[4, 8] Holt has fed carbohydrate labeled with isotopic tracers to premature infants and has found that the absorption is more than 95 per cent.[9] Another series of studies showed that the absorption of fat was quite variable in the premature infant and that many of the calories being fed as fat, especially in the smaller babies, were lost in the stool.[6, 10]

Levine and Gordon therefore advocated a feeding mixture which was high in protein, high in carbohydrate, low in fat, and approximated 120 calories for every 150 c.c. of fluid. They carried out a carefully controlled clinical study with such a formula and found, in comparing the weight gains of small premature infants fed human milk,

an evaporated cow's milk formula, or a special formula prepared from half skimmed milk with added carbohydrate, that the small infants grew best on the modified half skimmed milk formula (prepared commercially as Alacta; Dryco is another prepared milk with essentially the some composition).[11]

At the time these studies were being conducted, similar observations made at other institutions were generally in agreement with the findings of Levine and Gordon, except in one important area. Holt and co-workers believed that the amount of fat in the diet could be maintained at approximately the levels found in evaporated milk if the animal fat was removed from the original milk and in its place unsaturated fatty acid fats were substituted.[12, 13] From data accumulated in disorders in which there is fat malabsorption it has been shown that unsaturated fatty acid fat is better absorbed than saturated fatty acid fat.[14] Gordon was not convinced in his trials with milk formulas containing olive oil that there were consistently adequate absorptions.[10] Both groups agreed therefore that a high protein milk was useful, and that carbohydrate was well tolerated, but Levine and Gordon advocated the half skimmed milk preparation with added carbohydrate, and Holt utilized a preparation in which olive oil had been substituted for the animal fat (Olac).

We have recently had occasion to study fat absorption from various feeding mixtures.[15] It was found that in prematurely born infants weighing between 1,500 and 2,000 grams, the absorption of fat with Olac was adequate and that the formula is well tolerated. However, there have been changes in the Olac formula since its initial preparation. It had been shown by Holt and his co-workers that unsaturated fatty acid fats were better absorbed than animal fats but not all to equal extent.[12, 13] For example, corn oil was better absorbed than olive oil. The current preparation of Olac is made from defatted milk with corn oil added instead of olive oil as in the earlier formulations. It is possible that had Levine and Gordon used the currently available Ola there would have been greater agreemen between their data and those of Holt. Clinically babies appear to do equally wel on either milk when they are prepared i the same concentrations and fed in approximately the same amounts to babies o comparable ages and weights. In order to evaluate the adequacy of high or low protein concentrations in the formulas it is necessary to provide calories from other sources in feedings low in protein. These oils are useful for this purpose.

The quantity of protein allowances in the feeding of premature infants has been considered in recent years in relation to renal dynamics. Gordon, an advocate of high protein cow's milk feedings, observed in 1951 that some infants developed edema when they were changed from diets of human milk to diets of cow's milk containing equivalent amounts of protein, fat, carbohydrate, and water, suggesting that more sodium and fluid were being retained on the cow's milk formula.[16] Cow's milk, and specifically its protein, is much higher in mineral and ash content than is human milk. As a result in the last few years a number of questions have been posed regarding the concept of feeding cow's milk with its added electrolyte content to premature infants and also regarding the amount of protein which it is safe, or necessary, to feed such infants irrespective of the source of the protein. This argument has also been extended to the protein requirements of full-term and older infants.

The importance of this issue is not completely academic. In the first place it is important to know what the tolerance of the premature infant is for protein. Second, if the protein requirements for optimal nutrition, especially for full-term newborn and older infants and for children, are lower than those that have previously been defined, this would prove a boon to those areas in which protein is less plentiful than in the United States. An important question in relation to the problem of renal solute

load is whether the significant limiting factor on kidney function is the concentration of protein in the formula or whether it is simply the amount of protein ingested irrespective of the quantity of water consumed with it.

Talbot and his co-workers introduced the concept of safe limits for renal excretion; by studying individuals in various states of health they were able to work out certain limits beyond which they believed it unsafe to go either in the administration of fluid or of solutes.[17-19] They defined the maximal renal diluting and concentrating powers. The maximal renal diluting power in infants, premature as well as full-term, does not appear to be markedly different from that of adults, and the limit which is suggested is in the neighborhood of 20 c.c. per milliosmol of solute, or a formula 6 to 7 times as dilute as serum. On the other hand, the ability to concentrate urine presumes active work on the part of the kidneys. Maximal efficiency requires, therefore, that the kidneys be mature enough to carry on this function and that the entire individual, and especially his kidneys, be in a state of good health. The normal adult can concentrate urine so that approximately 0.7 c.c. of fluid can be utilized to excrete one milliosmol of solute. Thus urine may be about 4 times as concentrated as serum. The young infant, with his immature kidney, is able to do only about half as well, so that he needs about 1.4 c.c. of fluid for each milliosmol. The premature infant with his immature renal tubular concentrating power cannot concentrate even to these levels under many conditions and it would therefore appear to be unsafe to administer fluids orally or parentally which would require concentration perhaps to more than 4 or 5 c.c. of fluid per milliosmol. Under certain conditions, the urine might be expected with maximal concentration to be less concentrated than serum. This suggests that the osmolarity of the feeding should not exceed the ability of the kidneys to excrete their contained solutes.

One of the first reports to throw some light on this subject was that of Pratt and Snyderman; they evaluated the renal water requirements of premature infants who were fed 2 evaporated milk formulas.[20] The first formula consisted of evaporated milk with added Dextri-Maltose and water, with only 14 per cent of the calories supplied as protein, almost 50 per cent as carbohydrate, and 36 per cent as fat. The second formula was made up of evaporated milk and water without added carbohydrate. Approximately 20 per cent of the calories were supplied as protein, 28.5 per cent as carbohydrate, and 51.5 per cent as fat. In each formula the caloric concentration was 0.9 calorie per cubic centimeter or 27 calories per ounce. On each of these feedings the renal solute load was handled well in infants but the osmolar concentrating power of the kidney was so taxed with the unmodified evaporated milk, or 20 per cent protein feeding, that the authors believed the renal solute load was high enough to be dangerous if the baby suffered from any degree of dehydration. The authors did not believe that the solute load of the high protein feeding would be dangerous if it were offered in more dilute form, that is at 0.7 calorie per cubic centimeter. No comment was made regarding the safety of a formula of 20 per cent of the calories derived from protein and the intermediate concentration of 0.8 calorie per cubic centimeter as in the Alacta feedings recommended by Levine and Gordon.

This work was extended in a study by Kagan.[21] Human milk which had been manually expressed and pooled was fed to one group of infants, breast milk and a skimmed cultured cow's milk in a ratio of 4:1 was fed to a second group, Similac was fed to a third group, and an Alacta Dextri-Maltose formula was fed to a fourth group. All of these formulas were fed in quantities so that the infants took approximately 80 calories per kilogram per day, which is considerably less than the 120 calories recommended by Levine and Gordon. With these feedings, the infants who received human milk had the lowest gain in weight, 7.9

grams per kilogram per day; the highest gain in weight was 11.5 grams per kilogram per day in the infants fed Alacta. Kagan pointed out that there was greater gain in weight on Similac, in which the protein offered was only 2 Gm. per kilogram per day than on the modified human milk in which the infants were offered almost 2.5 Gm. per kilogram per day. He believed that the differences in weight gain could not be explained on the basis of increased protein content, otherwise the weight gain of infants fed the skimmed milk enriched formula should have exceeded that of those fed Similac. He believed that the improved gains with Similac could be correlated with a higher ash content of this preparation than that of human milk or of the modified human milk formula. He extended this argument in assuming that the high weight gain by the infants fed the Alacta formula could likewise be correlated with the markedly higher ash content of this high protein feeding derived from cow's milk. Furthermore, he took the data of Levine and Gordon in which infants were fed 120 calories per kilogram of body weight and pointed out that among these children the differences in weight gains previously attributed to differences in the proportions of protein, fat, and carbohydrate could also be correlated at these caloric levels with the ash content of the diet.

At the present time these arguments of Kagan cannot be fully answered on the basis of available data. It is quite possible that the increased weight gain observed by Levine and Gordon is in some way correlated with the increased ash content of the Alacta feedings and is partly related to edema formation. This would not appear to be so from their observation that the water retention–weight gain ratio was constant at 65 per cent in both the cow's milk and human milk fed groups.[4] In addition, as pointed out by Gordon in a recent review on protein requirements, it does not seem justified to attribute the increased weight gain noted with the Alacta feedings to increased ash content alone when the feeding mixtures also differed in protein and fat content.[22] Wallace and co-workers have pointed out in their studies on albino rats that increased gain in weight on high protein, high electrolyte intakes was correlated with proportionately increased protein content of the body.[23] The animals which were fed varying protein and electrolyte intakes varied in terms of weight gain and in their clinical courses. However, the compositions of the bodies with regard to water, protein, and ash content were quite consistent despite differences in over-all growth on various diets.

The difficulties produced by Kagan's report are twofold. First of all, it clearly poses questions which require answers. It should not be difficult to conduct clinical studies in human prematurely born infants which could be adequately controlled to distinguish the possible differential effects on growth of varying intakes of protein and electrolytes. Such data are not available. Second, perhaps as a result of this report, or coincident with it, multiple questions regarding protein intake have been raised. Some of these are related to the species from which the milk as a source of protein is derived. Holt, in particular, has raised questions regarding the concept of "optimal" amounts of protein intake.[24, 25] He has quite validly questioned whether the most that an individual will tolerate of a foodstuff is necessarily the optimal amount. Holt, Gordon, and others have also questioned the validity of the currently employed bases for evaluation. Specifically, in dealing with prematurely born infants, is it growth per se in which we are interested or should it be survival, development of adaptive enzyme systems, or other as yet undescribed parameters of measurement?[22, 24-27]

Perhaps a clue to the answer of the problems of protein concentration and mineral content in the diets of prematurely born infants is supplied by the recent interesting observations of Edelmann and co-workers.[28, 29] They have demonstrated that the response of prematurely born infants to the stress of dehydration may vary with the protein content of their preceding diet

Infants fed a high protein diet were able to concentrate urine to a much greater degree than those fed a low protein diet under the same conditions of dehydration. Such infants could secrete urine with the same osmolar concentration as adults, a feat previously thought to be impossible. It is possible that this observation explains Gordon's and Kagan's previous observations that a few infants might become edematous when fed cow's milk feedings with a high renal solute load after having previously been on low solute human milk feedings. Prior to the work of Edelmann and Barnett, although the influences of renal function were considered, little attention was paid to the possibility that this function might vary depending on the order of introduction of the different diets.

In conclusion it can be emphasized that no dietary plan for premature infants is in an unquestioned position at this time. There are many unanswered questions. More effort must be expended to define the goals and the meaning of terms such as "adequate" and "optimal" and on the design of experiments to test these concepts than on trying to win additional support for work previously carried out in relation to high or low protein regimens in the feeding of prematurely born infants. The purpose of this article as stated at the outset was not to provide a comprehensive review, but rather to examine critically some of the principal features now under study.

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# *Historical notes on parenteral fluid therapy of diarrhea in infants*

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EARLY accounts of "watery gripes" in infants were extremely sketchy with regard to treatment, and dealt principally with speculations concerning the etiology. From the time of Hippocrates through the era of the Medieval pediatrists, brief medical writings concerning diarrhea in infants dealt mainly with the use of herb concoctions and poultices made of bizarre materials. During the sixteenth, seventeenth, and eighteenth centuries these primitive therapeutic measures were used uniformly without convincing evidence of success. Fatality rates were uniformly high, and survival depended mainly upon the efficiency of the infant's intrinsic defenses against disease.

The first really systematic account concerning diarrhea in infants was that of Benjamin Rush[1] who summarized early nineteenth century thought as to etiology and treatment. He outlined a seven-point program of therapy which may be summarized as follows: (1) evacuation of bile from the gastrointestinal tract by induction of emesis and by purging, (2) administration of opiates for "composing the bowels" and for pain relief, (3) demulcent and diluting drinks such as herb tea, (4) clysters of flaxseed tea, or mutton broth, or starch suspended in water, to which was added a few drops of opiate, (5) plasters of Venice treacle applied to the epigastrium and flannels dipped in infusions of bitter and aromatic herbs in warm spirits, or Madeira wine applied over other areas of the abdomen, (6) administration of "tonic and cordial medicines" such as port wine, claret, or various herb beverages in the postacute stage of the disorder, and finally, most important of all, (7) exposure to country air.

In gaining knowledge of the physiology of body fluids, practicing physicians as well as chemists and physiologists have played an important role. Initially the body fluids were studied only in relation to cholera and somewhat later in relation to diabetic coma and to diarrhea in infants. The parenteral administration of body fluids had its beginning in 1667 when Denys[2] carried out one of the first blood transfusions in man. The work of Denys followed immediately upon the heels of experiments by Richard Lower who had accomplished direct transfusion of blood from one animal to another. Salt solutions were

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not used in medicine, except as purgatives, for many years after the introduction of blood transfusion techniques.

The real beginning of fluid replacement therapy may be traced to a brief letter from a London physician to *Lancet* in the year 1831. This letter outlined the findings of its author, Dr. W. B. O'Shaughnessey, regarding deficiencies of water, neutral saline, free alkali, and excesses of urea in the blood of patients with severe cholera. Mention was also made of the increase in the amount of salts, especially carbonate of soda, present in the stools of these patients.

Although Dr. O'Shaughnessey eventually described his findings in more detail, meanwhile a Scotch research opportunist, Thomas Latta,[3] made the first clinical application of this work. Using a solution containing 0.4 per cent sodium chloride and 0.3 per cent sodium bicarbonate (approximately an isotonic solution), Latta treated a number of adult patients with cholera. He and his contemporaries lacked cognizance, however, of the relationship of water loss to circulatory failure. Fortunately in their concern in supplying sufficient sodium salts they inadvertently covered the water requirement and achieved remarkably good clinical results. Weatherhill[4] and Miller[5] in 1832 likewise applied this new form of therapy for cholera and reported gratifying results. Even the enthusiasm of these physicians, coupled with the valiant editorial support of *Lancet,* was incapable of surmounting the wave of ridicule and vicious criticism of many colleagues who failed completely to understand the rationale for this new form of supportive treatment. Consequently, when cholera again invaded London 20 years later, the treatment reverted to bleeding, sweating, poulticing, and purging.

While the utilization of parenteral fluids sank into ignominy, strides were being made in the laboratories of German scientists. Notable among these workers was Carl Schmidt who performed remarkably complete analyses of the blood, stools, and vomitus from healthy human subjects and from patients afflicted with cholera.[6] Using the ponderous chemical methods of the times, this skilled and careful worker and his collaborators recorded values amazingly similar to those achieved by modern laboratories. Their analyses required some 200 ml. of blood obtained by venesection, a fantastic quantity in the light of present-day concepts of pediatric laboratory analyses.

Modern theories regarding acidosis had their beginning with the discovery, by a French investigator named Boussingault,[7] that large amounts of ammonia frequently appeared in the urine of patients with advanced diabetes. Some writers have credited this discovery to Hallervorden,[8] a German scientist whose contributions consisted mainly in repeating and confirming Boussingault's work. The German scientists of the day probably chose to ignore Boussingault's investigations, as well as those of others outside their country, in a jealous effort to guard their position of pre-eminence in scientific endeavors. Shaffer[9] subsequently showed that Boussingault's technique was distinctly superior to those of his contemporaries.

The classic work of Bidder and Schmidt[10] describing the characteristics of the body fluids along with the contributions of earlier investigators, enabled Claude Bernard in 1859 to promulgate the concept of the internal environment and its influence in health and disease.[11] Fagge[12] in 1874 applied the observations made in cholera patients to the treatment of diabetic coma and focused attention upon dehydration as a part of the clinical picture in these patients. At about the same time Kussmaul[13] recorded the first clinical description of "air hunger" in advanced diabetic patients. His description was classical, describing the deep, pauseless pattern of respiration which has long been used as a clinical sign of severe metabolic acidosis. Several years later the clinical observations of Walter[14] suggested that alkali injections would reverse the physiologic effects of inorganic acids. These observations were later confirmed in the laboratory by Minkowski[15] who described the first good analytic method for the demonstration of reduced base bicarbonate in the blood. Stadelmann[16] in 1883

set forth the "acid intoxication" theory and first used the injection of a pure alkaline solution (2 to 3 per cent sodium carbonate) in the treatment of diabetic coma.

An Italian physician, Cantani, who was probably unaware of O'Shaughnessey's work 60 years earlier, confirmed the blood chemical findings of his predecessor in patients with cholera and applied them clinically during an epidemic in Naples.[17] Again a number of clinicians became enthusiastic about the use of saline injections, but their recommendations remained unheeded in the face of criticism by the German physicians. These severe critics had found parenteral fluid therapy to be ineffective in their own hands, probably because of their failure to provide patients with quantities of fluid sufficient to repair dehydration.

General acceptance of parenteral fluid therapy was finally achieved during the early part of the twentieth century as a result of the investigations of Rogers[18] in India and of Sellards[19] in the Philippines. The severe acidosis of cholera was first documented by Sellards, who performed direct measurements of plasma bicarbonate. Development of other analytical methods by such eminent biochemists as Haldane, Priestly, Folin, Van Slyke, Benedict, and many others, paved the way for the second great era in parenteral fluid therapy.

This second great period, the years between World Wars I and II, was heralded by L. J. Henderson's[20] contributions in elucidating mechanisms of the human body's defense of neutrality. Application of this knowledge was carried out by a host of workers in the various clinical fields. Although most of the early work in the use of parenteral fluids had been done in connection with cholera, the similarities between this disease and other diseases associated with diarrhea became readily apparent. The term "intestinal intoxication," introduced earlier by Finklestein to describe the clinical picture produced by severe diarrhea in infancy, slowly became a meaningless term as the associated physiologic disturbances became better understood.

Misconceptions which had arisen earlier, such as the belief that the relative quantities of fluid and electrolytes were preserved despite large losses of water and salt from the gastrointestinal tract, began gradually to be dispelled. Detailed studies of the chemical composition of diarrheal stools of infants were made by Holt, Courtney, and Fales.[21] As a result of the work of Howland and Marriott[22] and Schloss and Stetson[23] describing the acidosis occurring concomitantly with diarrhea of infancy, attention became refocused upon the use of sodium bicarbonate in fluid therapy.

Replenishment of blood circulatory volume began to receive its due attention after Blackfan realized that his and Howland's patients had been receiving too little salt solution. He initiated the use of the intraperitoneal route in order to facilitate the administration of larger volumes of saline, which he felt would overtax the circulatory system if given entirely by the intravenous route.[24] The classical work of Marriott[25] showed the perilous effects of dehydration upon the circulation of the blood. At about the same time Schloss[26] published his work relating the effects of impaired renal function upon the composition of the body fluids. While these basic advances were being made, ideas regarding physiologic disturbances accompanying diarrhea in infants centered about the presence and action of toxic substances absorbed from the gastrointestinal tract. As a means of ridding the body of these "toxins," the technique of exsanguination transfusion was developed by a group of Canadian physicians.[27, 28, 29] This procedure, a formidable one even in the present era, never received wide acceptance and was eventually abandoned in favor of other therapeutic measures.

By the mid 1920's, parenteral fluid therapy had become established upon an irreproachably scientific basis, and the mortality from severe diarrhea during infancy had dropped from approximately 90 per cent to about 10 or 12 per cent.[18] Concepts regarding the role of noxious substances absorbed from the gastrointestinal tract began to be discarded. Powers,[30] in outlining his famed "compre-

hensive plan" of treatment of infantile diarrhea in 1926 wrote of the "so-called intestinal intoxication." The comprehensive plan of Powers centered around four main points: namely, the administration of parenteral fluids, blood transfusion, withholding of oral feedings for a period of time, followed by gradual reinstitution of feedings via the alimentary tract. This plan of treatment for infantile diarrhea was one of the first of a number of such didactic plans to appear in modern pediatric literature.

In 1932 Hartmann and Senn[31] diverted attention from the prevalent practice of administration of sodium bicarbonate to correct states of acidosis by describing the effects of sodium racemic lactate. In their report they pointed out several disadvantages of sodium bicarbonate: (1) excessively rapid correction of acidosis, (2) difficulty of sterilization while maintaining the desired pH, and (3) disturbances of ionic balance between Na, K, Ca, and Mg. Sodium racemic lactate was offered as an effective substitute for sodium bicarbonate without the disadvantages listed. In a subsequent article Hartmann and associates[32] related further experiences in the use of sodium racemic lactate and stated that even moribund patients appeared to metabolize this organic salt in an efficient manner. Their report described a 50 per cent survival rate in a group of infants suffering from very severe diarrhea.

Beginning in the third decade of this century attention began to be directed toward evaluating losses from the intracellular fluid compartment, along with changes in the extracellular compartment. Butler and coworkers[33, 34, 35] pioneered in describing some of the intracellular fluid and electrolyte losses accompanying diarrhea, and later provided data regarding daily maintenance requirements in infants and children. Other definitive studies, including Gamble's classic studies on the life raft ration,[36] were also performed delineating the bodily losses sustained during starvation and during dehydration with acidosis or alkalosis. These investigations enabled a much more accurate estimation of the therapeutic needs of dehydrated infants than had been previously possible.

Although potassium losses during diarrhea had been recognized for a number of years, a generalized fear surrounded its use as a therapeutic agent until 1946. At that time Darrow[37] described his classic investigations concerning the magnitude of potassium losses, both intracellular and extracellular, in infants with severe dehydration due to diarrhea. After observing improved results from its oral administration, potassium was then included in fluids infused by parenteral routes.[38, 39, 40] This innovation in therapy produced a marked decline in the mortality rate in infants with severe diarrhea. During the past 15 years the use of potassium in many clinical situations has received widespread acceptance for the most part. Hartmann and his group, however, remain as the champions of a minority group which feels that there is no need for including potassium in parenteral fluids in concentrations exceeding 4 or 5 mEq. per liter, the concentration normally found in the extracellular fluid. Their therapeutic regimen, however, includes early institution of potassium.

With the advent of World War II, a great surge of investigation occurred in the field of fluid and electrolyte physiology. This increased research effort has been directed mainly toward investigations of shifts of fluid and electrolyte between extracellular and intracellular fluid compartments, toward more definitive determinations of the magnitude of these compartments, and toward studying the body's utilization of water and various ions in health and in diverse clinical disorders.

Only the foundations have been laid for our understanding of the basic physiology of cells and their environment. Undoubtedly a multitude of exciting discoveries awaits physicians, investigators, and practitioners alike, in the realm of body fluid dynamics and in their application to diagnosis and therapy. As our knowledge of the body fluids becomes more thoroughly integrated, surely we shall recognize, along with Claude Bernard, that "... there is no separate science of medicine or physiology, there is only a science of life."

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# CLINICAL PATHOLOGICAL CONFERENCE

## THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

*Sidney Farber, M.D., Editor*

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EIGHT months prior to his first Children's Hospital Medical Center admission, this 13-year-old boy had localized pain in the region of the lumbar spine, following strenuous exercise in the gymnasium class. While the pain was severe, he could walk, and in 1 to 2 hours the acute symptoms subsided. Following this there was tenderness but no actual pain, and there were no other symptoms.

One month later he was hospitalized elsewhere for 3 days because of persistent tenderness of the spine. The history disclosed that 4 years before he had fractured a small toe when he accidentally kicked a rock, and 2 years before he had sustained three fractures of the wrist, twice on the right and once on the left, each time associated with trauma. The fractures apparently healed uneventfully and no comment was made then concerning the radiologic appearance of the bones. At the time of this 3 day hospitalization, he was asymptomatic but noted to be "quite kyphotic." Physical examination was otherwise negative except for a Grade III systolic murmur, loudest posteriorly on the left, and questionably lower blood pressures in the legs than in the arms. X-ray of the spine showed "marked osteomalacia." The serum contained: calcium 11.8 mg. per cent; alkaline phosphatase 7.7 Bodansky units; albumin 4.7 Gm. per cent; and globulin 2.7 Gm. per cent. A 24-hour collection of urine contained 100 mg. per cent calcium. Routine urinalysis was "negative," and an intravenous pyelogram was normal. A chest x-ray showed questionable calcification of the aortic arch. With these findings, the patient was referred to the Adolescent Clinic for an opinion regarding his metabolic and cardiac status and, after examination, hospitalization was advised for further evaluation.

Both parents and a 10-year-old sister are well. His maternal grandfather had multiple fractures of the shoulder and hip, each associated with trauma, and his stature was also kyphotic. A maternal great-grandfather had questionable bone disease and diabetes. The paternal grandfather was hard of hearing; he died of cancer of the prostate. The maternal grandmother had arthritis with marked scoliosis, the latter since childhood. She died of a cerebral hemorrhage at 56 years of age.

Pregnancy with this child was uneventful. Labor was "short" with delivery complicated by breech presentation. The birth

weight was 7 pounds, 6 ounces. He was given oxygen. There were four convulsions during the first few days of life. After this initial period, however, he improved and had no further difficulties. Formula was fed without difficulty; the appetite was always good, and sometimes excessive. Vitamins were given until one year prior to admission.

His development was not otherwise remarkable. He walked at 16 months. He was of average height, but overweight, especially after 9 years of age. There were no school problems and no serious illnesses, but an appendectomy was performed when he was 12 years old. He has had strabismus since the age of 2, with myopia requiring glasses after the age of 6. Emesis occurred about once fortnightly. There was no polyuria.

On admission here the temperature was 99° F., pulse rate 84 per minute, respirations 24 per minute, blood pressure 112/70 mm. Hg., height in the third percentile, and he was 51 pounds heavier than the average for his height. He was a pleasant and cooperative obese 13-year-old boy, with marked dorsal kyphosis. The skin had a normal texture and there were no striae or bruises. Visual acuity was poor and the sclerae were bluish white. There was increased anterior-posterior diameter of the chest, with a Grade II systolic murmur along the left sternal border. The lungs were clear. The abdomen was protuberant but the liver, spleen, and kidneys were not palpable. There was adolescent development of the genitals with pubic but no axillary hair. The testes were descended. There were no tenderness over the spine and no limitation of motion. Neurological examination was negative.

**Laboratory studies.** The blood contained: hemoglobin 13.5 Gm. per cent and 7,800 leukocytes per cubic millimeter with a normal differential count. Urinalysis showed a specific gravity of 1.022, pH 5.5, and albumin, sugar, and microscopic examination normal. Serum chemistry determinations were as follows: nonprotein nitrogen 24 mg. per cent; pH 7.52; sodium 140 mEq. per liter; potassium 3.9 mEq. per liter; chloride 102 mEq. per liter; carbon dioxide content 24 mEq. per liter; calcium 9.8 mg. per cent; phosphorus 3.7 mg. per cent; alkaline phosphatase 8.1 Bodansky units; cholesterol 230 mg. per cent; albumin 5 Gm. per cent; and globulin 2.6 Gm. per cent. Urinary 17-hydroxycorticoids were 2.9 to 5.0 mg. per 24 hours, and 17-ketosteroids 3.2 to 5.7 mg. per 24 hours. Two-day intravenous ACTH test (25 mg. intravenously for 8 hours) showed a rise of 17-corticoids to 23.7 and 31.4 mg., and of 17-ketosteroids to 10.4 and 8.6 on the first and second days, respectively.

Urinary FSH (follicle stimulating hormone) was positive at 5 to 10 m.u., and negative at 20 m.u.

X-ray of the long bones and dorsolumbar spine showed "marked osteoporosis involving all of the bones sufficiently severely to allow bi-concave collapse of all dorsal and lumbar vertebrae. Intervertebral spaces are preserved." No clear evidence of cardiac abnormality was recognized radiologically, although some question of left ventricular enlargement was raised.

The patient was asymptomatic throughout hospitalization. Cardiac consultation suggested that there was no significant heart disease. After initial laboratory studies, an operation was performed.

Dr. Anne P. Forbes.* This 13-year-old boy entered the hospital with the complaint of intermittent backache of 8 months' duration. There was a history of a little more than the expected number of fractures for a normal, active boy. It is significant that he fractured the same bone twice, because when fractures are purely accidental, one expects them to be a little more scattered. The fractures apparently healed uneventfully and no comment was made then concerning the radiologic appearance of the bones.

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Two years before he had back pain he was asymptomatic but kyphotic; he presumably already had back disease, as evidenced by osteoporosis on x-ray examination.

One would like to know whether he was developing and growing normally at the time of his prior admission elsewhere.

As concerns his grandfather, if the term "fracture of the hips" refers (as is usually the case) to fracture of the neck of the femur, it would be absolutely diagnostic of pathologic bone. If this grandfather were the age of George Bernard Shaw, the osseous lesion would be osteoporosis of old age. If he broke his hip when he was not a very old man, however, he had abnormal bone in his hip, because a young man with good bones never breaks the neck of the femur.

There is a fairly definite history of bone disease in other male members of the maternal side of the family. This is all that is necessary to establish the hereditary nature of the disease, so that one is only mildly interested in the deafness on the paternal side and one questions whether muscle, joint, or bone disease was primary in the maternal grandmother.

The boy was obese. As obesity becomes more and more common in the population, the significance of obesity in medical history becomes less important, but those who grow up overweight start getting obese at approximately 9 years of age. Therefore, this is an age at which the insignificant or medically nonsignificant type of obesity begins. If it is significant, then he has had a disease since the age of 9.

His height is in the third percentile. If he is "folded-up," or kyphotic, and he has lost 2 or 3 inches, this would not indicate that he failed to grow, and that is quite important. We would much rather know his growth curve than a single measurement. We would like, then, to know what his span is since it would probably be normal and therefore a closer measure of the true skeletal growth.

He does not have polycythemia or polymorphonuclear leukocytosis. Urinalysis is normal. The slightly high serum pH of 7.52 may be disregarded in view of the fact that the sodium, potassium, and chloride are normal and the serum carbon dioxide is low normal.

At the outside hospital, the 24-hour urinary excretion of calcium was 100 mg., which I believe is abnormally high for a child but normal for an adult. It has often been our experience at the Massachusetts General Hospital that abnormally high values for calcium in the outside hospital become normal values in our own. This determination seems to be one most open to error in any of the common laboratory procedures. I think he has a normal calcium level.

Acid phosphatase was not determined until later, when it was probably influenced by the treatment that I am told he is receiving. Acid phosphatase is reported as 9 Guttman units, apparently a high value for his age. However, the phosphatase has not been further tested to determine whether or not it is of prostatic origin. Possibly some of this high acid phosphatase is of nonprostatic origin. Almost by accident, we found one of our prepubertal boys with osteogenesis imperfecta to have excessive acid phosphatase. I know of only one mention of this in a note in *Lancet* a few years ago.[1] The mechanism of this needs to be worked out, especially since it may turn out to be a useful diagnostic test.

The adrenal function is normal at the base line, and normal under ACTH stimulation. His urinary FSH is just what it should be for an adolescent boy.

Evidence of cardiac abnormality is too nebulous to require comment radiologically or clinically, and the patient was normotensive. I believe that the aorta is included in the statements concerning his cardiovascular state.

As I analyze the disease, this boy had severe osteoporosis of the spine. By osteoporosis we mean a loss of bone due to a disorder of matrix formation. This is as evident clinically as it is by laboratory test, in that he has had relatively little bone pain, which is

much more characteristic of osteoporosis than it is of the osteomalacia, or of any invasion of bone by neoplastic tissue. The fact that his spine is most severely involved again indicates osteoporosis rather than osteomalacia. If this boy had any one of the disorders of metabolism leading to osteomalacia I would expect him to have bowing of the legs or deformity of the pelvis prior to severe deformity of the spine. His history of progressive loss of height and kyphosis, together with one episode which probably represents vertebral collapse with very little pain and no neurological disease, indicates that, clinically, he has some disease of the bony matrix.

Normal calcium, normal phosphorus, and normal alkaline phosphatase substantiate this concept of deficient matrix. There is also good evidence that his disorder can be inherited. One should not overlook some fairly outspoken metabolic defect. The major metabolic cause of osteoporosis, namely, Cushing's syndrome, was very carefully excluded. Of course, one arrives at the diagnosis of Cushing's disease by looking at the patient, and you cannot do that from reading a case history, but apparently he did not have the appearance of Cushing's syndrome. This is confirmed by the adrenal tests. He is short in height and a failure of growth can be due to Cushing's syndrome. In fact, one of the earliest symptoms in a child who develops Cushing's syndrome is that growth stops about as soon as he starts to gain weight. This boy would have had to have Cushing's syndrome from the age of 9, or at least from the age of 11, if that were his diagnosis, and the other features of the condition should be much more obvious. This is particularly true when the syndrome appears before puberty since it is then almost always due to a tumor and runs a more striking course than when it is associated with hyperplasia of the adrenals. I think we can discount Cushing's syndrome as a cause of his osteoporosis and simply choose between those inheritable defects of the bony matrix which would explain the symptoms of the several members of his family, as well as the fragile bones of this patient.

The three types of defect which I might mention are: (1) hereditary metaphyseal dysplasia; (2) neurofibromatosis, and, (3) osteogenesis imperfecta. Of the three, the only one I would want to diagnose is osteogenesis imperfecta. With neurofibromatosis, one sees scoliosis and kyphosis, or fractures due to cysts in the bones. This boy has none of the typical skin manifestations, and neither are they mentioned in any member of the family. Moreover, there is no mention of scoliosis. The bones that he broke seemingly appeared normal; his fractures apparently did not occur through "cysts" as might be the case if fractures were due to neurofibromatosis. Moreover, he had not broken the tibia, which is a common site of fracture in this condition. I would, therefore, think that neurofibromatosis is a poor choice to explain the osseous disorder in this family. Hereditary metaphyseal dysplasia may present as a fracture of the spine. In the one family with this disease known to me (it is exceedingly rare), osteoporosis of the spine with compression fracture was quite an outstanding feature. On x-ray, the classical abnormal shape of all the bones, the failure of remodeling, and the enlargement of the ends of the bone, which confirm the diagnosis, were apparent. I think that this is an unlikely diagnosis in this boy. The lesion is diagnostic on x-ray and I would expect him to have more trouble with long bones than with the spine. I think it is possible for osteogenesis imperfecta to present as a spinal disease. The very severe instances of this disease usually are present at birth, or before. In less severe forms there are all degrees of involvement, down to quite unrecognizable bone disease.

I have seen several patients with osteogenesis imperfecta who have perfectly normal bones by x-ray; one knows that they have the disease despite the normal x-rays because they have repeated fractures, as do other members of their family. Moreover, some of those patients with very mild disease cease to have fractures of long bones at

puberty but begin to develop much more severe osteoporosis of the spine at the same time.

I have in mind a boy, the exact age of this patient, who fractured long bones eleven or twelve times, up to the age of 11 years. When I saw him he was nearly 13 and had had no further fractures; in the interval, puberty had started. The long bones were perfectly normal by x-ray, but he presented for back pain, rapid loss of height, and very severe osteoporosis of the spine, comparable to that seen in Cushing's syndrome. His mother had had fractures which stopped at puberty, but immediately following the menopause she developed very severe osteoporosis relieved by therapy with estrogens. He had other relatives with classical osteogenesis imperfecta, with deformities of all bones. Later I discovered that this has been a fairly common type of clinical progression in other cases when spinal osteoporosis became more severe, coincidentally with accelerated growth at puberty.

I suppose one can fit these observations into some of the pathologic anatomy of osteogenesis imperfecta. Cartilage is normally built and normally calcified. The defect lies in the transformation of cartilage into normal bone and this process should normally be accelerated at puberty. However, this does not clearly explain why the spinal disease progresses and the lesions of the long bones appear to improve: could this be related to some difference in the ages of maturation of the different bones? After cessation of growth there is time for slow remodeling of the imperfect bone so that the patients have less trouble than they did as children. That is what I think will happen in the patient under discussion.

I have just been told that the boy is receiving testosterone which presumably will hasten and telescope his period of growth and epiphyseal maturation. This might make him worse for a few months while he grows more rapidly, but it will get him over the period where the osteoporosis is severe.

I have treated a patient with estrogen so as to slow his growth, as well as shift his metabolism in a way known to be anabolic for bone formation. I do not know how your patient is doing, but my boy is doing very well; the collapse of the spine stopped and, in spite of estrogen administration, which I think is an inhibitor of growth hormone, he is growing much more than he grew before. He runs the risk of infertility. This risk is taken only because there is such a very high proportion of such severely affected members in the family that they do not feel it would be a tragedy if this boy were unable to pass on the trait and to father crippled children.

**Fig. 1.** Marked osteoporosis with collapse of vertebral bodies involves the lumbar spine (left), and films of the knee show normal bone age and some evidence of osteoporosis (right).

I think this patient has osteogenesis imperfecta.

DR. E. B. D. NEUHAUSER. We have one film from the outside hospital, taken 2 years ago, showing one of the wrist fractures.

DR. FORBES. Is this a Colles' fracture, or the kind of greenstick fracture seen in normal children?

DR. NEUHAUSER. It is not a Colles' fracture. It is more like that of a normal child. Colles' fracture in a child of this age is really an epiphyseal displacement, and here we have a fractured bone in the epiphysis that is normally aligned with the metaphysis.

Unless we are being misled by the fact that this wrist was immobilized for previous fractures, there was definite porosis

at that time. A skull film was made at the age of 10 years and, while it is not clearly osteoporotic, the bone certainly appears to lack some of the densities that we would expect to see. These changes in the skull are not nearly as marked or definite as may occur, especially in younger more severely involved patients.

DR. FORBES. Are the teeth developing normally? One boy I have been following has marked dentinogenesis imperfecta.

DR. NEUHAUSER. The teeth seem essentially normal.

In a film of the knee made a year ago (Fig. 1), there is definite osteoporosis; his bone age corresponds to the normal standard; the metaphyseal architecture looks good; there is no defect in modeling. There are no cystlike lesions and no erosive lesions to suggest any other disease. Films of the spine show similar changes in all portions, best seen in the lumbar area (Fig. 1). The vertebral bodies are quite radiolucent and washed out, with no well-defined trabeculae. In other words, here we do not need the "cue" of change in contour which we so often use unconsciously to help us recognize change in density.

The margins are fairly dense and quite sharply defined, and certainly in addition to the total diminution in the height of the body there are biconcave deformities with relative expansion of the intervertebral spaces. Generally, there is accentuation of the lordosis and the kyphosis, but there is no scoliosis.

DR. SHERWIN KEVY. Why was a determination of FSH done?

DR. JOHN F. CRIGLER. I was interested in whether or not there would be a gonadal defect occurring in a male. Acute osteoporosis may occur in gonadal dysgenesis as the patient gets older. Have you ever seen this in a eunuchoid male?

DR. FORBES. Very definitely in elderly eunuchoid males, but not before puberty.

DR. CRIGLER. Would this apply in pubertal gonadal dysgenesis? Usually osteo-

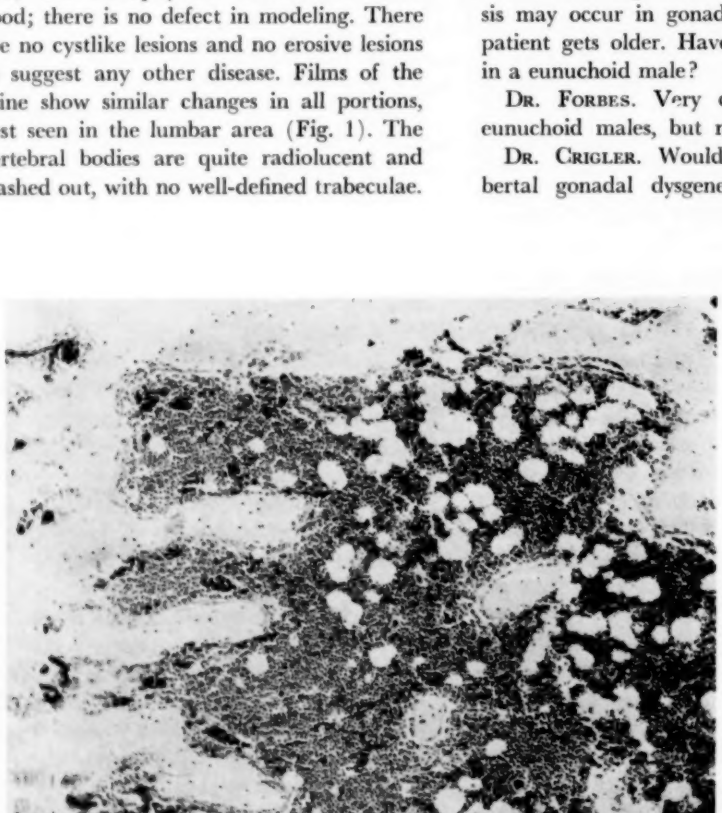

**Fig. 2.** Costochondral junction at left, metaphyseal cortex at top, and definite decrease in bony spicules in the spongy bone. A continuous layer of flattened osteoblasts surrounds each bone spicule. The cartilage cell columns are regular and orderly but the zone of provisional ossification gives the impression of inactivity. (Toluidine-blue eosin. ×130; reduced ¼.)

porosis with gonadal dysgenesis begins at 12 or 13 years of age, even though gonadal function supposedly is not very great.

Dr. Forbes. I have not seen it. We have had very few patients that young in an adult clinic.

Dr. Neuhauser. Something like Turner's syndrome, perhaps? Of course, that was the question raised here, at first.

Dr. Gordon F. Vawter. The operation which was performed included biopsy of a portion of rib and costochondral junction.

As predicted, the pathologic findings are compatible with the diagnosis of *osteogenesis imperfecta tarda,* or, in other terminology, perhaps with *familial juvenile osteoporosis.*

Grossly, the zone of provisional ossification is quite regular, but narrow and relatively inconspicuous. A measure of the thinning of the cortical bone is that the red color of the normally fleshy dark red marrow is transmitted through the bone to give an unusual dark blue color. Although the bony portion is quite flexible (probably abnormally so) it fractured quite sharply, suggesting that calcium deposition was plentiful.

Microscopically (Fig. 2), the costochondral junction is regular and smooth, with cartilage cell columns as long as in a control of the same age, but rather abruptly there is a quite marked deficiency of medullary (and cortical) bone, most evident in what would normally be the zone of provisional ossification, giving wide marrow-filled spaces between a few scattered small spicules of bone.

At high-power magnification there is no evidence of increased numbers of osteoclasts to suggest unusual resorption of bone and each spicule is ringed by a row of flat or low cuboidal osteoclasts so as to preclude deficiency in the number of these cells. In short, the picture is one of a deficiency in bone matrix without evidence of imperfect mineralization, without abnormal resorption, or without deficient numbers of osteoblastic cells. A failure of matrix formation is implied.

The picture here differs from that of a severe neonatal or infantile form of the disease where obvious histologic abnormalities in matrix are demonstrable. Here we did not find fibrillar matrix or abnormal deposits of PAS-positive or metachromatic intracellular material, which have been described, although many staining procedures were carried out to assess these possibilities. This need not alter the diagnosis, however. These differences between the pathology of the severe infantile and of the milder states with delayed recognition, as in this case, have occasionally been encountered by others.

Dr. Crigler. Dr. Forbes, we have been as lucky as you. The patient is subjectively improved, so much so that he volunteers for activity which I think may still be somewhat excessive, although the most recent x-rays, a few days ago, show improvement, and he has no bone tenderness. Balance studies have shown tendency to retention of calcium, phosphorus, and nitrogen, while he has been receiving Nilevar. So far, there have been no untoward side effects.

Dr. Neuhauser. Osteoporosis is still evident in the long bones and spine. Improvement in the spine is quite striking, with increase in height of vertebrae and quite apparent increase in density.

Dr. Jonathan Cohen. In osteogenesis imperfecta there is more than just an absence of bone or what you might call a matrix defect, the defect being less than we should see. I do not believe there has ever been a clear-cut definition of what the defect in matrix might be in this disease. Under the electron microscope the matrix (or what there is of it) seems perfectly normal, but histologically these bones are far from normal.

There are often no Haversian systems in the cortex and the trabecular systems are not organized as one would expect, so that there is also an organizational defect. There have not been many good studies of osteogenesis imperfecta along functional endocrine lines.

In this patient, symptoms warranted a bit more investigation and I think modern methods in endocrinology are carrying us

one step further to eliminate another source of our confusion.

DR. VAWTER. Dr. Jerome Gross of the Massachusetts General Hospital has studied the skin of this patient and, so far, has not been able clearly to demonstrate abnormality in collagen or its organization in this patient, this in spite of the fact that many patients with osteogenesis imperfecta have more generalized or multiple organ involvement, including peculiarities of the skin.

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# COMMENTS ON CURRENT LITERATURE

## *Polyneuronitis: Guillain-Barré syndrome*

THE LANDRY-GUILLAIN-BARRÉ syndrome is a well-recognized clinical condition characterized by progressive involvement of the nervous system with varying degrees of motor and sensory disturbance. However, its existence as a distinct entity has been questioned on the basis that it may represent an allergic phenomenon, and because its occurrence has been reported in association with a number of diseases of divergent etiology. The earliest neuropathologic findings in patients dying with this condition appear to be consistent with the proposed allergic etiology. According to Haymaker and Kernohan,[1] and to Schienker,[2] the outstanding feature early in the disease is marked edema of the nerve fibers of the spinal roots and the proximal portions of the cranial and peripheral nerves. Schienker described a similar edematous involvement of the spinal cord tracts. The pathology underlying the characteristic signs and symptoms has been described in detail by Berlacher and Abington.[3] "The axonal edema with consequent sudden increase in bulk of most of the spinal roots leads to narrowing and obliteration of the perineural spaces and, if more severe, to strangulation of the radicular trunks."[3] Degeneration of the myelin sheath follows, and the loss of nerve function results in an areflexic flaccid paresis or paralysis associated in some instances with sensory disturbances. Retrograde cellular and myelin sheath degeneration are thought to account for the inflammatory process in the peripheral nerves and the central nervous system. According to these authors, "obliteration of the perineural spaces blocks the absorption of spinal fluid along these channels and leads to stagnation and trapping of the fluid within the subarachnoid space. . . . The classic albumino-cytologic dissociation, almost universally observed in this syndrome, can be explained on the basis that this obstruction permits escape of water and electrolytes, but not the larger protein molecules."[3] Capillary damage and increased permeability are thought to be factors which allow leakage of protein into the spinal fluid. While normal spinal fluid cell count is usual because of minimal involvement of the meninges, lymphocytic pleocytosis may occur during the early stage of the disease.

The Guillain-Barré syndrome has been reported in association with many disease conditions including Cushing's disease, multiple myeloma, tuberculous meningitis, diphtheria, infectious mononucleosis, rubella, respiratory infections, etc. Some features of the condition suggest viral etiology while others do not. For example, equation of the essentially normal spinal fluid cell counts is difficult in the presence of possible viral infection of the central nervous system. It has been suggested that "a virus which has no primary cytopathogenic effect on nerve tissue proper could produce oedema of the brain stem, spinal cord, spinal nerve roots, and hyperaemia of the meninges that results in symptoms characteristic of this entity."[4] Kisch[5] in 1958 reported a case of Guillain-Barré syndrome following smallpox vaccination. This patient was an adult female who had been vaccinated on two previous occasions, initially at the age of 25 years with primary take, and revaccinated at 45 years of age

with the reaction described as an immune response. Four weeks prior to the present illness she had been vaccinated a third time at the age of 52. The reaction was described as a "severe primary take." Widespread inflammation of the vaccination site developed with redness and swelling of the surrounding area, marked general malaise, and a temperature rise to 102° F. Sixteen days following vaccination the patient noticed numbness of the hands, lower extremities, and the circumoral area. Pain in all the extremities and in the trunk musculature was severe. Weakness of the extremities, especially of proximal muscle groups, rapidly followed, and the patient was unable to stand or walk. Three weeks after vaccination she experienced difficulty in swallowing, and a few days later became incontinent of urine. There had been no history of neurological disorder in the past except two episodes of chorea associated with acute rheumatic fever at the ages of 8 and 20 years. There had been some evidence of allergic asthma as a child.

On admission to the hospital and during the subsequent clinical course, it was apparent that this patient was suffering from an "illness characterized by polyradiculoneuropathy involving motor as well as sensory components, and cranial as well as peripheral nerves."[5] The signs and symptoms included bilateral facial weakness, flaccid quadriparesis, loss of deep tendon reflexes, and peripheral sensory changes, with very slow recovery. "The cerebrospinal fluid showed the albuminocytologic dissociation considered to be an important identifying feature of the syndrome."[5] Kisch reviews the evidence supporting the concept that the Guillain-Barré syndrome represents a hypersensitivity reaction. He points out that the condition has been known to follow the administration of antirabies prophylaxis, typhoid-paratyphoid vaccine, tetanus antitoxin, pertussis and antipneumococcic vaccines, as well as the administration of human serum. In one recorded instance, a severe hypersensitivity reaction of the Gulliain-Barré type was associated with the use of para-aminosalicylic acid (PAS) in the treatment of tuberculosis.[6] According to Kisch,[5] the occurrence of this syndrome following smallpox vaccination has been recorded on at least two previous occasions.

Two recent reports dealing with the Guillain-Barré syndrome are of special interest. The first of these reports by Parker, Wilt, Dawson and Stackiw[4] concerns the isolation of a strain of ECHO virus type 6 "from the feces and cerebrospinal fluid of a ten-year-old boy with clinical and laboratory findings which conform to the criteria laid down for the diagnosis of Landry-Guillain-Barré syndrome." Seven days prior to the onset of the illness, the child had complained of a sore throat, and the mother noted swelling of the anterior neck on both sides. The illness was considered minor, and the boy appeared to have recovered completely within 2 or 3 days. A week later, however, he was complaining of extreme fatigue and numbness and tingling of the fingers and toes. It was noted at this time that the left eyelid was drooping. Within a few hours the patient developed marked muscular weakness which was progressive. On admission to the hospital the boy was afebrile, but the general muscle weakness was extreme. Examination revealed bilateral seventh nerve weakness and left fifth motor nerve weakness; the patient was areflexic except for the abdominal and plantar responses. Two days later marked respiratory distress developed requiring emergency tracheotomy; paralysis of the muscles supplied by the ninth and tenth cranial nerves became marked, and the patient's general condition deteriorated rapidly, paralysis being almost complete by the afternoon of the second hospital day. He was transferred to a negative pressure tank-type respirator and hydrocortisone (as Solu-Cortef) therapy was instituted: 200 mg., intravenously, per day in divided doses. Improvement began 4 days later with the return of function to the ninth and tenth cranial nerves, followed shortly by improvement in function of the other cranial nerves. With this improvement steroid therapy was reduced in dosage gradually, and was discontinued in 21 days' time

Recovery was slow but steady, and physical examination performed 2½ months after the original illness revealed no residual abnormality. This boy's history was not remarkable; he had had chickenpox and measles in childhood without complication. Smallpox vaccination and Salk vaccine for poliomyelitis, with administration of the full series, had been accomplished without incident. There was no history of allergy, recurrent infection, or familial illness.

Laboratory findings on the day of hospital admission showed cerebrospinal fluid under pressure of 110 mm. of water; there were fewer than 5 cells per cubic millimeter; protein value was 16 mg. per cent, sugar 80 mg. per cent, and chlorides 730 mg. per cent. Subsequent lumbar punctures yielded spinal fluid values which were not essentially different. By means of monkey-kidney and human-amnion cell cultures, a cytopathogenic agent was recovered from both cerebrospinal fluid and fecal specimens, this agent being identified by appropriate means as a strain of ECHO virus type 6. Neutralization tests employing acute and convalescent serum samples were carried out against the newly isolated ECHO-6 and against a stock strain of ECHO virus type 6. The acute-period sample showed a titer of 1:4 against both virus strains, the second serum sample a titer of 1:8. In view of this low titer, tests for antibody to poliovirus type 1, and to herpes simplex virus were performed. The majority of persons in this age group show reasonably high titers to these viruses even under steroid therapy. These titers, 1:8 for poliovirus type 1, and 1:4 for herpes simplex virus showing low concentration of antibodies, paralleled the low concentration for the ECHO virus strain. This observation raised the question of a serum protein abnormality. Electrophoretic examination revealed that alpha-1 globulins were absent from both serum specimens and that the gamma globulins were below the normal level. These electrophoretic values were compared with control values from normal subjects. The authors are inclined to believe that the failure to develop significant rise in titer of antibody to the ECHO virus may have been the result of steroid therapy.

The other recent report concerning the Guillain-Barré syndrome appears in the *New England Journal of Medicine*. This article by Osler and Sidell[7] has as its purpose a clarification of the diagnosis of the condition, and emphasizes the need for exact diagnostic criteria. These authors point out that in the past many types of acute polyneuritis have been included under this syndrome. They believe, however, that one group of cases obeys certain strict diagnostic criteria and has a characteristic clinical picture, course, and prognosis. On the basis of 10 cases of the Guillain-Barré syndrome with findings given in tabular form, Osler and Sidell summarize the significant signs and symptoms which in their opinion distinguish this condition. In all 10 cases dysesthesias were present in the early stages; symmetrical paralysis occurred in all the patients and progressed after their admission to the hospital; and in all, the tendon reflexes were reduced or absent. An increased protein content in the cerebrospinal fluid was observed on admission in 9 of the patients, and in the tenth a few days after admission. Pleocytosis was not observed, the highest spinal fluid cell counts being six cells and five cells. In 7 of the 10 patients no cells were observed in the spinal fluid specimen. The authors are of the opinion that while recovery may be slow in the Guillain-Barré syndrome, the prognosis in general is good.

From such recent publications it is clear that at present a large number of illnesses of varied pathology falls under the classification of acute polyneuronitis. Among these, a group of cases, patients with "typical" clinical course, has been designated by the eponym, Guillain-Barré syndrome. In general, the etiology remains obscure. The recent report of this condition associated with ECHO-6 virus infection is of considerable interest and importance in that eventually the continued search may yield definitive etiological diagnosis in certain cases of polyneuronitis.

RUSSELL J. BLATTNER, M.D.

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# Books

**Heritable Disorders of Connective Tissue.** Second edition. Victor A. McKusick, M.D., St. Louis, 1960, The C. V. Mosby Company, 333 pages. Price $12.00.

This is the second edition of a book which was first published in 1956. The first edition was limited and based on a series of articles which appeared in the *Journal of Chronic Diseases*. The current volume has been considerably enlarged and includes 80 additional illustrations and 100 pages of additional text. The literature since preparation of the first edition has been surveyed and the additional rich experience of the author enhances the authoritativeness of the volume.

The book is divided into 8 chapters: (1) The Clinical Behavior of Hereditary Syndromes, (2) The Biology of Normal Connective Tissue, (3) The Marfan Syndrome, (4) The Ehlers-Danlos Syndrome, (5) Osteogenesis Imperfecta, (6) Pseudoxanthoma Elasticum, (7) The Hurler Syndrome, and (8) Concluding Comments. Chapters 3, 4, 5, and 7 are of special interest to the pediatrician. There is a historical survey and a discussion of clinical manifestations, incidence and inheritance, differential diagnosis, and the basic defect for each disorder.

There is probably no other single source extant that covers the material in this volume more completely or more authoritatively. Some concept of the vast experience of the author is given by noting that McKusick collected 74 kinships with the Marfan syndrome in 6 years. There are about 200 affected individuals in these pedigrees and 33 of these affected families are represented in Figs. 3 to 38. The survey of the Ehlers-Danlos syndrome is based on a personal study of 14 kinships, each with at least 1 affected member. The description of the Hurler syndrome is based on personal experience with 20 patients. This large number of clinical observations combined with the review of the literature results in a detailed description of each entity with the proper perspective given to nuances and variants. A rather complete list of references at the end of each chapter and complete annotation of the text makes the book very useful as a reference source.

The historical notes are most interesting and include little gems such as previously unpublished photographs of the original patients with the Hurler syndrome described by Hunter in 1917, an excellent photograph of Antoine Bernard Jean Marfan (Parisian professor of pediatrics), and a reproduction of a skeleton with osteogenesis imperfecta from Vrolik, 1849. It would be remiss to fail to mention that the frontispiece is a superb previously unpublished crayon drawing of Sir Archibald E. Garrod to whom the book is dedicated.

The book is very readable and contains many little-known facts that will maintain the interest of everyone from medical student to academician. This book is highly recommended to anyone with an interest in the disorders therein described.

ANGELO M. DI GEORGE, M.D.

**Il Gargoilisimo.** Giuseppe Falchi and Mario Midulla, Rome, Italy, 1958, Il Pensiero Scientifico, 349 pages. Price 3,500 lira.

This book is the result of the authors' meticulous study of the Hurler syndrome (gargoylism). The preface is by Professor Gino Frontali. Almost one half of the book (123 pages) is devoted to the presentation of the details of 11 patients with this syndrome who were studied by the authors. This is followed by an analysis of 172 cases collected from the literature. Symptomatology, laboratory studies, radiographic changes, differential diagnosis, and etiology are discussed and statistically analyzed.

Falchi and Midulla found an incidence of consanguinity of 16 per cent in the 172 patients. They demonstrate that the majority of Italian persons with the syndrome have been reported in "regional foci" where the incidence of inter-

marriage is relatively high. They point out that the incidence of consanguinity in the parents of female patients was more than double that found in males. These authors refute Nja's hypothesis of the existence of a sex-linked recessive form of the Hurler syndrome (a variation of gargoylism in males with clear corneas). They present evidence that corneal opacity is dependent on the duration of the illness as well as on the sex of the patient. They also point out that certain other changes such as hepatomegaly, kyphosis, and changes of the sella turcica appear earlier in males than in females but that the disease has a more rapid course in females, with the average age at the time of death being about 2½ years earlier than it is in males.

There are 27 pages of statistical tables and an appended tabulation of the 172 cases used in this study showing the various characteristics analyzed.

Although the book is in Italian it should be of great value to those with a particular interest in the Hurler syndrome. It is worth while pointing out that none of the Italian literature on the Hurler syndrome reviewed in this book can be found among the references listed by McKusick (see above).

ANGELO M. DI GEORGE, M.D.

**Biochemistry of Human Genetics.**
Ciba Foundation Symposium. G. E. W. Wolstenholme and Cecilia M. O'Connor, editors, Boston, 1959, Little, Brown & Company, 347 pages. Price $9.50.

On its tenth anniversary, the Ciba Foundation has organized for the first time a conference in a place other than in its home in London. This symposium was initiated by Professor Montalenti of the Institute of Genetics, University of Naples, where the conference was held. Among the 29 participants were the following nine Americans: B. Childs, H. Eagle, V. M. Ingram, H. A. Itano, H. M. Kalckar, J. Lederberg, S. E. Luria, J. V. Neel, and S. W. Wright.

Following the introduction by L. S. Penrose on genetic analysis in man, the papers are presented in 3 groups. The first group, genetic control of metabolism, includes chapters on hereditary galactosemia, and the genetics of primaquine sensitivity. The larger part of the symposium deals with the abnormal human hemoglobins, fetal myoglobin, plasma proteins, haptoglobins and transferrins, and blood group substances. Finally, there is a chapter on the mechanism of gene action.

This symposium is of the usual high standards of the previous Ciba Foundation Symposia which have served as models for interdisciplinary conferences. This volume makes an excellent companion piece to Harris' book (see above), which deals with the known, whereas this one deals with the periphery of the known. Academic pediatricians will find much of interest in this volume.

ANGELO M. DI GEORGE, M.D.

**Human Biochemical Genetics.**
H. Harris, M.D., New York, 1959, Cambridge University Press, 310 pages. Price $7.00.

This book is a sequel to Dr. Harris' previous book *Introduction to Human Biochemical Genetics,* published in 1953. To quote from the first sentence in the introduction, "This book is about inborn differences between human beings. More particularly it concerns those differences which can be formulated in biochemical terms." L. S. Penrose points out in the foreword that it is difficult to keep pace with the rate with which biochemical discoveries are being made and that Dr. Harris has not attempted to present the very latest views in every detail. "Dr. Harris has minimized this disadvantage by devoting the book mainly to the description of well-authenticated material, leaving out speculative interpretations of anomalies which are, so far, not well understood."

There are 10 chapters dealing in succession with aspects of Mendelian heredity in man, amino acid metabolism, variations in carbohydrate metabolism, the human hemoglobins, the blood-group substances, the plasma proteins, some miscellaneous inherited disorders of metabolism, and the problem of gene action.

On every page one perceives the expertness of the author by the clarity of treatment of the subject with which he is dealing. Many of the disorders which are not yet well delineated or are still speculative have not been included, but one looks forward to the growth of this text in subsequent editions. The last chapter on the problem of gene action may be too cursory for the bio-

chemist but is well done and the explanation of the Watson-Crick hypothesis is one of the more lucid ones that this reviewer has read. Selected references at the end of each chapter are up to date and the text is annotated. One feels completely confident in recommending this book to anyone interested in human genetics or biochemistry or to any pediatrician interested in inborn errors of metabolism. Considering the price of books in general this volume is modestly priced.

ANGELO M. DI GEORGE, M.D.

**Child Development; Physical and Psychologic Growth Through Adolescence.**

Fourth edition. M. E. Breckenridge, and E. L. Vincent, Philadelphia, 1960, W. B. Saunders Company, 648 pages. Price $6.50.

Physicians, nurses, dentists, and social workers meet children at important crises in their lives; whatever they do with children carries permanence by reason of vividness and dramatic excitement. Even a single contact with a doctor, nurse, dentist, or social worker may leave a lasting impression on the child's attitudes and feelings—favorable if the professional person understands the child and approaches him skillfully, unfavorable if the reverse is true. A knowledge of child development can be profitable both to the child and to the professional worker.

On the basis of over 1,400 items in the bibliography, the majority of which are dated from 1955 to 1960, this book has been brought up to date in both the physical and the psychological aspects of growth and development. Considered are the effects of heredity, prenatal environment, the endocrines, prematurity, illness, physical defects, drives and motivations, moods, adult attitudes, the broken as well as the normal home, competition within families, the influence of schools, churches, camps, and other agencies.

There are 80 new illustrations which include many graphic line drawings made especially for this edition. New sections cover: current findings on *brain damage* as an influence on growth; the effects of *radiation* on growth; and *race* as a cultural effect on the development of children.

AUTHORS

**First International Conference on Live Poliovirus Vaccines.**

Sponsored by the Pan American Health Organization and the World Health Organization, with the cooperation of the Sister Elizabeth Kenny Foundation, Washington, D. C., 1959, Pan American Sanitary Bureau, 713 pages. Price $5.00.

This volume contains the papers presented and the discussions held at the First International Conference on Live Poliovirus Vaccines in Washington, D. C., June, 1959, with 61 scientists from 18 countries in attendance.

The general topics under which the specific papers were read were: General Considerations and Evaluation of Live Poliovirus Vaccines; Criteria of Attenuation, Development, Selection, and Testing of Poliovirus Strains for Use in Field Trials; Properties and Behavior of Orally Administered Attenuated Strains; The Problem of Interference in Live Poliovirus Immunization and Field Trials.

**Pathology of Infancy and Childhood.**

Agnes R. Macgregor, Edinburgh and London, 1960, E. & S. Livingstone Ltd. (The Williams & Wilkins Company, Baltimore, in the U.S.), 631 pages. Price $14.50.

The author, who has had vast experience in the subject of this book, states in the preface that it is her purpose "to present in a volume of moderate size an account of the morbid anatomy and histopathology of disease in infancy and childhood." Therein lies the difficulty, for the subject is large; and rather than being of moderate size the book is distinctly small, resembling a handbook or synopsis of pediatric pathology—taking up topics and treating each in almost cursory fashion. For example, the subject of rickets is dealt with in two short pages presenting what is generally known and certainly what is to be found in most comprehensive textbooks on general pathology. Hepatolenticular degeneration is given but a single paragraph.

This brevity characterizes the entire work. The book was intended primarily for pathologists but also for pediatricians and students. For any of these, however, the material presented is too limited. There is so much more the author could

have brought to bear—out of the literature as well as from her own material—on almost any of the topics approached.

The references are too few and, unfortunately, as in most British publications, do not contain the titles of the articles included.

For the most part the writing is concise, clear, and accurate but occasionally becomes confusing as in the discussion of atelectasis. It is stated that this lesion may be primary or secondary, but then within the same paragraph ". . . for atelectasis is not a primary disease."

The work is well illustrated. There are many excellent photographs of both gross and microscopic lesions, the majority of which are from the author's cases. Color plates of good quality and diagrams are scattered among them.

The pages are small with a shiny surface and the print is large, making the text easy to read. Its small size makes it handy for quick reference.

In summary, the single shortcoming of this terse, accurate, compact, meaty little manual is its brevity. One could wish only that there were more of it.

MARIE VALDES-DAPENA, M.D.

**Cancer and Allied Diseases of Infancy and Childhood.**

Irving M. Ariel, M.D., and George T. Pack, M.D., editors, Boston, 1960, Little, Brown & Company, 605 pages. Price $22.50.

This book, a compilation of the work of 27 contributing authors, is concerned primarily with the clinical aspects of neoplasms in early life. It is a major contribution to the literature and is worthy of careful perusal by anyone dealing with this subject.

As is proper, a number of diseases which cannot be considered as cancer are included. One might question, however, the need for such an extensive section dealing with hyperplasia of the adrenals in a book of this nature, and the subject of nonneoplastic enlargement of the breast, although admittedly an important one, is possibly given undue emphasis in a volume of this size. Somewhat less than one-half of the chapters are written by authors whose principal activities are concerned with pediatric problems, and this probably accounts for the fact that such rare pediatric tumors as chondrosarcoma and giant cell tumor of bone are discussed in almost as much detail as is Ewing's tumor. Certain lesions which are of real concern to the pediatric oncologist, moreover, are either entirely omitted or are dealt with in only a cursory manner, e.g., lymphosarcoma of the bowel, rhabdomyosarcoma of the orbit, and hemangioma of the parotid.

As is apt to be true of a book written by multiple authors, a certain number of contradictions are present in the text. For example, although in one section it is stated (correctly) that a large proportion of hemangiomas regress spontaneously, this important fact is given almost no emphasis in another section dealing with the treatment of these lesions. Similarly, in one section the emphasis is placed on conservative therapy of congenital sternocleidomastoid tumors, while in another section surgical excision appears to be the treatment of choice of most such tumors.

Errors are bound to appear in a book of this length, and this one is no exception. For example, in the section on neuroblastoma the statement is made that "the younger the patient the worse the prognosis," when actually the reverse appears to be true. The statement that "carcinoma of the prostate has not been observed before the age of seventeen years" is also an error. One might also question the statement that many hepatic tumors are benign and are amenable to therapy as well as the omission of any comment concerning irradiation of the thymus in the section dealing with carcinoma of the thyroid.

In spite of the above criticisms, this book is a valuable one and provides a convenient and complete reference to the subject of neoplasms in infants and children. The more than 2,000 references which are included in the bibliography, most of them relatively recent ones, would alone make this volume of interest to any physician concerned with the diagnosis and management of neoplasms in early life.

JAMES B. AREY, M.D.

**Advances in Pediatrics, Vol. XI.**

S. Z. Levine, editor, Chicago, 1960, The Year Book Publishers, Inc., 285 pages. Price $9.00.

This is the eleventh of an excellent series on particular pediatric problems. The chapters and respective authors are "Respiration and Respiratory Problems of the Newborn Infant" by C. D

Cook, H. Barrie, and M. E. Avery; "Clinical and Experimental Interrelations of Sodium and the Central Nervous System" by Robert E. Cooke and Edward J. Ottenheimer; "Allergy in Childhood" by William C. Deamer; "Infantile Diarrhea and Dehydration: Ambulatory Treatment in a Hydration Center" by Julio Meneghello, Jorge Rosselot, Carmen Aguiló, Fernando Monckeberg, Oscar Undurraga, and Mario Ferreiro; "Aminoaciduria and Certain Related Disorders of Amino Acid Metabolism" by Selma E. Snyderman and L. Emmett Holt, Jr., and "Present Status of Hormone Therapy in Rheumatic Fever, With Special Reference to Short-Term Treatment in Active Carditis" by May G. Wilson.

# *Correspondence*

*To the Editor:*

It is with some concern that I read the paper on "Abdominal Epilepsy" by Drs. Sheehy, Little, and Stone in the JOURNAL, March, 1960. Recurrent attacks of abdominal pain in children have long been unclear in their etiology even after intensive study by many radiographic and laboratory examinations. A number of studies of children with abdominal pain have been reported as showing only infrequently a specific organic etiology. Through the years a number of investigators have attempted to define an entity labeled "abdominal epilepsy" as the basis for abdominal pain in some patients. As stated by the authors, the criteria for this diagnosis have involved (1) a history of recurrent attacks of abdominal pain accompanied occasionally by headache or other signs as syncope, (2) some degree of electroencephalographic deviation from the normal pattern, varying from a very borderline to clear-cut epileptiform changes, and (3) finally, a response to diphenylhydantoin therapy varying from decreased to complete disappearance of symptoms. Some authors have stated that the typical clinical picture and the response to therapy are sufficient to establish the diagnosis in the presence of normal electroencephalographic findings.

Thus far, since there has been no clear distinction made of the clinical picture of abdominal epilepsy from the remainder of patients with such symptoms, the diagnosis, in essence, rests on the response to therapy. I believe that it is no longer valid to report a study on "abdominal epilepsy" in this day without having a large enough series of cases set up in treatment, utilizing the double blind control technique. Recent studies with placebos have clearly indicated the need for sophisticated studies controlling both the bias of the physician and the hope of the patient. In one such control study on abdominal pain by Apley, no distinct effect from therapy was evident. Recent study of a large group of patients with abdominal pain of considerable severity and frequency has indicated that a surprising number show considerable to almost complete disappearance of the symptomatic complaint following a period of intensive physical and psychological study during hospitalization. Such an experience with these patients, without specific pharmacologic therapy, would appear to be similar to that attributed by the authors to diphenylhydantoin therapy in their group.

Furthermore, the problem of precise definition of the significance of minimal to moderate "abnormalities" in the electroencephalogram is one which has distressed many pediatric services. Apley, in his fine book *The Child With Abdominal Pain*, was unable to discover a different incidence of electroencephalographic abnormalities in a large series of children with recurrent abdominal pain and children free of abdominal pain. If such observations can obtain further confirmation, the diagnostic specificity of the electroencephalogram becomes considerably diminished in this context.

The cases which are presented as illustrations by the authors raise some interesting questions as to etiology. In Case 1, V. B.'s mother and some members of her family are described as having a history of peptic ulcer. In Case 2, the patient's mother is stated to have had a "nervous breakdown requiring psychiatric treatment." These brief descriptions about the mothers showing reactions traditionally having some connection with emotional disturbance raises the question of how the emotional state of the children is related to their symptoms. The lack of description of the children in these 2 cases makes one wonder whether the authors have any data in the behavioral area for both family and patient. On intensive psychological study our patients with abdominal pain seem more and more to have related disturbance of their feeling state. Although it is exceedingly difficult to quantify such observations, it does appear to us that emotional relationship to such visceral pain requires inclusion in the differential diagnosis as well as any other anatomic or functional abberation of neurological or intraabdominal pain. I do not wish to segregate any neurological relationship to the

emotional state but rather to emphasize by this distinction the importance of certain qualitative and quantitative aspects of environmental experience which may be of considerable diagnostic and therapeutic importance to the patient.

My concern with the term "abdominal epilepsy" is not whether such an entity may or may not exist. It is highly possible that these attacks of abdominal pain may have a multiple etiology including neurological aspects. Any pediatrician knows too well the impact of what it means to a family to label a child with some kind of epilepsy. One wonders how many children are receiving such a diagnosis on the basis of tenuous or vague diagnostic criteria. Certainly it is clear that the neurological basis for behavior is continuously undergoing more and more clarification and identification. One can question whether the kind of anatomic and physiologic considerations described by the authors clearly support the segregation of an entity which by inference (although never clearly stated) suggests some kind of specific anatomic or functional disturbance of the neurological system. There is great need for properly controlled studies with both psychological and neurological sophistication in this problem of abdominal pain. When the day of such studies arrives, perhaps only then will we be able to determine just what kinds of cases will fall into a group more precisely defined as "abdominal epilepsy."

GIULIO J. BARBERO, M.D.
PHILADELPHIA, PA.

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The doubts and caution expressed by Dr. Barbero concerning the diagnosis of abdominal epilepsy are in order and we are pleased to publish his letter. We agree completely that the diagnosis of abdominal epilepsy should be made only after most meticulous study to rule out any other possible cause and on the basis of the criteria listed by Sheehy, Little, and Stone (J. PEDIAT. 56: 355, 1960). Abdominal epilepsy, if it exists, is most probably a very rare disorder. It would, however, be a "head in the sand" editorial policy not to publish current data concerning it. We would add in the same vein as that of Dr. Barbero that a too ready tendency to assign the cause of recurrent abdominal pain to a psychological or a psychotic disorder is fraught with equal danger.

ED.

*To the Editor:*

The editorial by Dr. Ann G. Kuttner in the June, 1960, issue of THE JOURNAL OF PEDIATRICS on "Prevention of Rheumatic Fever Recurrences" raises a controversial issue. The editorial contains at least 2 unqualified and very positive statements which have yet to be substantiated. The statement, "It is now well established that prophylaxis for the prevention of streptococcal infections reduces the incidence of rheumatic recurrences," is undoubtedly true for short-term experiments under *ideal* conditions. How important this will be when the whole lifetime of the patient is considered has yet to be proved. It is entirely possible that we are merely postponing the rheumatic recurrence, not preventing it. The statement that monthly intramuscular injections of 1,200,000 units of benzathine penicillin is *foolproof* is true only if the patient is willing and able to return for these monthly injections. In a clinic setting we find many adolescents unwilling to do this.

Let me make it clear that at the present time I am in favor of a prophylactic program for rheumatic fever patients except for programs in which a new and more promising approach is being evaluated. The prophylactic program is the treatment of choice at the present time; however, at best, it is a most impractical and probably ineffective approach to the problem. There is some evidence that the use of penicillin prophylaxis will prevent the acquisition of immunity.[1-2] When this problem is added to the problem of "prophylactic break-through,"[3] it is plain that a continued search for more effective control measures is needed. The work of Lim and Wilson[4] is one such effort.

A far superior control measure would be obtained by the development of an adequate immunizing material which could be used to protect the patient against infection with Group "A" beta hemolytic streptococcus as can now be done for many other diseases.

This is a time for open-minded reasoning. Our emotional bias, our habits, and our blind prejudice must be avoided.

J. PHILIP AMBUEL, M.D.
COLUMBUS, OHIO

## REFERENCES

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*To the Editor:*

THE USES OF ABSURDITY
*or*
*Students, Doctors, and Ultramodern Therapeutics*

He is positively outdated who even remembers the days of courses in "Pharmacology and Therapeutics," when prescription-writing was indeed prescription-writing! I don't mean the old polypharmacy in mystic Latin, with "M. et ft. ungt.," or "Tal. charts. no." on the end. I mean when graduates in medicine relied upon pharmacists or apothecaries who wielded pestle and mortar and nicely balanced scales. Then physicians and pharmacists alike had to know their "incompatibilities"—a now happily forgotten word.

Nowadays druggists read off trade names from prescriptions, or "take" them over the phone, then pour solutions from big bottles into little ones, or more often hand out ready-filled bottles or boxes, with the doctor's name and directions copied thereon. Let it be cheerfully noted that what we now prescribe benefits the patient far more than did the "compounded-on-the-spot" mixtures of yesteryear.

Are the departments of pharmacology, medicine, pediatrics, etc., of our medical schools streamlined to keep up with the newer methods of dispensing "drugs"—for such we continue to call both antibiotic and chemotherapeutic agents. How do our medical schools and licensing boards go about evaluating the proficiency of their candidates in the all-important field of modern therapeutics?

Let them give heed to the following examples of "what might be," or "the shape of things to come," as they "set" examinations for the fledglings who must have proper healing in their wings:

*Comprehensive questions*

1. Name the 5 largest manufacturers of antibiotics. How do the salaries of their advertising managers compare with those of the average university or hospital investigators in the field of
   (a) Cancer?
   (b) Hematology?
   (c) Virology?
2. You are engaged in a clinical and statistical investigation of the efficacy of a certain company's broad-spectrum antibiotic preparation in the treatment of upper respiratory infections in your clinic and hospital.

   Do you swear (by Apollo and Panacea) to be completely impartial and objective in your evaluation of other competing commercial preparations?

*Questions from the micro-print*

1. You have just written a prescription for tablets of 6-chloro-7-sulfamyl-3, 4-dihydro-1, 2, 4-benzothiadiazine-1, 1-dioxide.

   For what condition or conditions should this medication be efficacious? What is its short and commonly used trade name?
2. Select any 5 of the following 8 advertised preparations, and give the chemical formula for each, together with the conditions for which each is indicated:
   (a) Plaquenil
   (b) Stelazine
   (c) Appetrol
   (d) Clariñ
   (e) Naturetin with K
   (f) Trilafon
   (g) Preludin
   (h) Tral 75 mg. Gradumet

The reader has recognized the foregoing for what it is: a *reductio ad absurdum* set forth to indicate a *trend.*

*The Lesson*

(For the physician who holds fast to the conviction that he and his profession exist for the benefit of the patient.)

We now have at our disposal remedies far exceeding in value anything our forebears ever dreamed of—remedies which *must* be produced in bulk by properly regulated and supervised commercial houses. Free enterprise being what it is, the doctor who gives his patient's welfare prime consideration should give well-nigh equal

place to the line from his Hippocratic oath: "I will reckon him who taught me this Art equally dear to me as my parents." For "him" we now read "Medical Faculty." Let the harassed physician keep in closer touch than ever with the ways and men of the medical school. For here he may expect still to find science, pure and undefiled. Here, he will gain the refuge he must have from the blandishments of those who sell. Here will be Brutus' "honesty to honesty engaged."

Valuable, essential as they are in "our way of life," the commercial houses must compete. What Hygeia was to Panacea, Advertising is to Free Enterprise: sister. And the Antidote to Advertising Run Riot is Sales Resistance.

*Conferences,* scientific meetings (yea, even those financed in part by these same commercial houses with their competing exhibits)—where truth and free speech prevail, and where facts are dispensed in profusion by those engaged in research and teaching—it is from regular attendance at such gatherings in hospitals and medical schools that the true physician will derive what he—and his patient—needs. The doctor who is too busy to go to such meetings, or to read his medical journals is—too busy. Even his medical journals, please note, are financed by the advertising, lurid at times, of the drug houses referred to above.

Now, more than ever, the physician must realize that others know more about many things than he does. They may be old instructors or new colleagues. He must keep learning from them "what's going on." He must let them help him keep his balance amid all the forces working upon him.

Modern developments practically require that we use trade names. None can keep all the complex chemical formulas at his tongue's end. None needs to be overwhelmed by the welter of advertising, nor by the suave, polysyllabic claims of "detail men." The hard-won principles of scientific medicine need not, must not, be abandoned.

PARK J. WHITE, M.D.
ST. LOUIS, MO.

# *Helmut P. G. Seckel, 1900–1960*

HELMUT SECKEL, M.D., professor of pediatrics in The University of Chicago School of Medicine, died April 13, 1960, following a coronary thrombosis. Dr. Seckel was born May 16, 1900, in Berlin, the eldest son of a family of scholars. His father was professor of Roman law and its foremost interpreter in the University of Berlin and a member of the Prussian Academy of Science. His younger, surviving, brother is a well-known scholar in the field of Japanese art and is professor of art history in the University of Heidelberg.

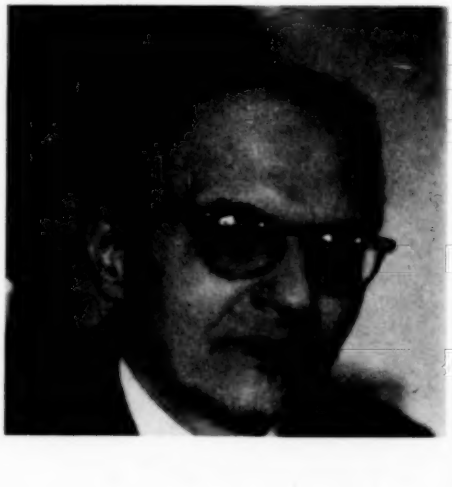
Dr. Seckel received his medical education at the University of Berlin and was trained in pediatrics by such renowned teachers as Czerny, Moro, and Kleinschmidt and was greatly influenced by Freudenberg.

His scholarly pursuits in his chosen field and his exemplary career at the University of Cologne were interrupted by the coming to power of the Nazis. He and his wife, Margaret, were driven from their beloved Germany by the Nazi scourge, leaving behind them family, friends, and the chaos which enveloped Germany.

He resumed his career in medicine when he joined the Department of Pediatrics of The University of Chicago School of Medicine in 1936. Here he worked until his untimely death at the age of fifty-nine.

Dr. Seckel will always be remembered as a scholarly man. In his scholarly pursuits he explored many fields: medical science, social science, art, philosophy, history, and theology. His readings and discussions in the field of existentialism were wide and profound.

*Reprinted from the Medical Alumni Bulletin of The University of Chicago by permission of the Editorial Board.*



Many felt he was old-fashioned because he respected the old German traditions, though he was appalled at the degradation to which the Nazi curse had led the German people. Yet his was an open mind, ever accepting of new ideas, the newest and most abstruse expressions of art, the newest advances in medical practice. He enjoyed the company of young people, colleagues and students, and was willing to learn from them.

He was a quiet man, a gentle man, a dignified man, yet humble and kind.

His contributions to science include many scientific papers in the fields of endocrinology, infectious disease, and growth and development. It was a happy occasion indeed for him to see his book, *Bird Headed Dwarfs, Studies on Developmental Anthropology,* published and given acclaim both in this country and abroad.

To all who knew Helmut Seckel, his passing leaves a great sense of loss for a scholar, a humanitarian, and a friend.

BURTON J. GROSSMAN

# News and notes

The following diplomates were certified by **The American Board of Pediatrics, Inc.,** at St. Louis, Missouri, on June 17-19, 1960:

Albo, Vincent Charles, 500 Parker Drive, Pittsburgh 16, Pennsylvania

Bertucci, Peter S., 621 Westwood Street, Mobile, Alabama

Bloom, John Edward, 1220 Kilby Terrace, Anniston, Alabama

Borchers, Justine, 412 West Hillcrest Avenue, Dayton 6, Ohio

Borenstein, Milton Kelter, 944 Agate Avenue, Anaheim, California

Bryan, George Thomas, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda 14, Maryland

Burns, William Thomas, 2719 North Olive Lane, Santa Ana, California

Copeland, John B., 1354 Longfellow Avenue, Chico, California

Davignon, André Louis, Fellow in Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota

Davis, David Campbell, 1100 West Pacific Coast Highway, Harbor City, California

Dietrich, Shelby Lee, 210 Orange Grove Avenue, South Pasadena, California

Dodson, Jerry Gene, Apt. 3 2302 West Beach, Biloxi, Mississippi

Dunaway, James Boyd, Box 1586, USAF Hospital, Keesler Air Force Base, Mississippi

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Jabbour, J. T., University Hospital, Minneapolis 14, Minnesota

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Ozaydin, Ismail M., 143 West Palmer, Council Bluffs, Iowa
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Richmond, H. John, 518 North Federal Highway, Lake Worth, Florida
Rubin, Sidney L., 419 Doctors Building, Omaha 31, Nebraska
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Sia, Calvin Chia Jung, 1305 Kalakaua Avenue, Honolulu 14, Hawaii
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Simon, William H., 1733 East Oklahoma, Enid, Oklahoma
Smith, Forrest Moseley, Jr., 132 Spanish Oaks Drive, San Antonio, Texas
Smith, George F., Jackson Memorial Hospital, 1700 N. W. 10th Avenue, Miami, Florida
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Tabellario, Carlo A., 1104 Sartori Avenue, Torrance, California
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Weatherhogg, Curtis R., 1023 Regent Street, Madison, Wisconsin
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Williams, Dana Steeves, Pediatric Service, Brooke Army Hospital, Ft. Sam Houston, Texas
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Wright, Harry Tucker, Jr., 536 Maple Street, San Diego 3, California
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Ziegler, William Lockwood, 915 South Colorado Boulevard, Denver 9, Colorado

The following passed their examination at previous sites but were not eligible to receive certificates until now:

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Branton, Leon Nelson, 1211 North 16th Street, Allentown, Pennsylvania
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Crump, James Leonard, 4531 North Boulevard, Baton Rouge, Louisiana
Danoff, Stuart J., 12013 Kemp Mill Road, Silver Spring, Maryland
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Felman, Alvin H., 1067 D 3rd Avenue, Dover, Delaware
Findlay, Prentiss Edwards, 1224 Manatee West, Bradenton, Florida
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Graham, Angus W., Jr., 2128 Somerset Avenue, Columbus, Georgia
Nasralla, Maridee Lee Knipmeyer, Hospital V. D'Antoni, La Ceiba, Honduras, C. A.
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Wood, David Eliab, 3301 North Charles Street, Baltimore, Maryland

*Special foreign certificates:*

Alejandrino, Lourdes Lardizabal, 19 Don Alejandrino Roces Avenue, Quezon City, Philippines
Anbari, Rachad, Children's Hospital, 1740 Bainbridge Street, Philadelphia, Pennsylvania
Carreon, Anita Torres, 363 Dalisay, Bacood, Sta. Mesa, Manila, Philippines
Chen, Hua-Chin, 711 Troy Avenue, Brooklyn 3, New York
Emmanouilides, George, c/o Mrs. M. Kondoprias, 1529 Roselyn Street, Philadelphia 41, Pennsylvania
Gharib, Reza, Nemazee Hospital, Shiraz, Iran
Gonzalez, Florentino A., Jr., 2697 Legarda Street, Manila, Philippines
Guzman, Gilda Maria, Manuel U. Gomez #51, La Vega, Dominican Republic
Guzman, Virginia Balderrama, Tagig, Rizal, Philippines
Hernandez, Antonio, Jr., P. O. Box 117, Davao City, Philippines
Hervada, Arturo R., 905 Clinton Street, Philadelphia 7, Pennsylvania
Ketusingha, Rambeya, 126 Ekamai Road, Prakanong, Bangkok, Thailand
Kim, Kee Hyun, c/o Miss Soon B. Choi, 1744 Columbia Road, N.W., Washington, D. C.
Ko, Kwang Wook, 8, 2-Ka, Yongsan-dong, Yongsan-Ku, Seoul, Korea
Levy, Micheline, c/o Mr. O. Levy, 5 Rue Fabert, Metz-Moselle, France

Martinez S., Ernesto, Driscoll Foundation, Children's Hospital, Corpus Christi, Texas
Matallana, Jorge E., Facultad de Medicina, Universidad del Valle, Cali, Colombia, S. A.
McAinsh, Walter Robert, 300 Longwood Avenue, Boston, Massachusetts
Rathi, Laxmi Kant, University of Virginia Hospital, Charlottesville, Virginia
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Sadili, Elisa V., 500 P. Leoncio, Sampaloc, Manila, Philippines
Santarina, Rosita Borja Cabanatuan City, Philippines
Seth, C. Kanta, 6/3 Original Road, Paharganj, New Delhi, India
Valdecanas, Leticia Q., Balanga, Bataan, Philippines
Viranuvatti, Pramote, 449/3 Raj-vi-thee Road, Bangkok, Thailand
Zentella, Raul Patricio, Calle 10 #909, Cordoba, Veracruz, Mexico
Zerrudo, Cenon D., Sara, Iloilo, Philippines

The **Southwestern Pediatric Society** has elected the following officers: President, John Wilcox, M.D.; Vice-president, Deron Hovsepian, M.D.; and Secretary-Treasurer, Harry O. Ryan, M.D.

The **Louisiana State Pediatric Society** elected the following as officers: President, Dr. J. Maxim Perret, Jr.; President-elect (Vice-President), Dr. Dorothy J. York; and Secretary, Dr. Ellen P. MacKenzie.

A **"Short Course in Audiology"** is offered several times each year by the Section of Audiology, Department of Otorhinology, Temple University School of Medicine. The course will last one week and will encompass theoretical and clinical aspects of audition. Hearing testing and interpretation will be stressed and office procedures, equipment, and industrial audiometry will be discussed.

For further information write to Philip E. Rosenberg, Ph.D., Director, Section of Audiology, Temple University Medical Center, 3401 North Broad St., Philadelphia 40, Pa.

Applications for the residency from July 1, 1961, to June 30, 1962, in **Pediatric Oncology at Memorial Center For Cancer and Allied Diseases** in New York City, New York, will be received up to Nov. 15, 1960. This residency is approved for partial credit by the American Board of Pediatrics and is limited to the neoplastic diseases of children. Salary is $3,600 annually plus maintenance. For application forms and information write: Director, Pediatric Service, Memorial Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.

Dr. Edmund P. Fowler of the College of Physicians and Surgeons, Columbia University, will present the **James Harkins Memorial Lecture on Problems in Pediatric Otology** before the Bronx Pediatric Society, December 14, at Morrisania Hospital, Bronx.

The **Miami Pediatric Society** has elected the following as officers for 1960-1961: President, Charles Rosenfeld, M.D.; President-Elect, George Lister, M.D.; Secretary, James A. Whiteside, M.D.; and Treasurer, Maurice Blinski, M.D.

**The Skin and Cancer Hospital of Philadelphia** announces the third annual postgraduate course in Pediatric Dermatology for pediatricians, dermatologists, and generalists. Emphasizing diagnosis and treatment of common cutaneous diseases in infants and children, the course will be presented November 14 to 18 at The Skin and Cancer Hospital of Philadelphia, Unit of the Department of Dermatology, Temple University Medical Center. Registration fee is $100.00. For information write Carroll F. Burgoon, Jr., M.D., The Skin and Cancer Hospital, 804 Pine Street, Philadelphia 7, Pa.

The organizational and scientific meeting of the **Southern Society for Pediatric Research** will be held October 29 and 30 at Vanderbilt University School of Medicine. The aims of the new organization will be to promote basic and clinical research oriented toward the field of pediatrics in the southern region and to serve as a forum for those interested in pediatric education. The meeting will be open. Full- and part-time members of pediatric departments, practitioners, and residents are invited. Membership will probably be elective. For information contact Dr. Mildred Stahlman, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville 5.

# EDITOR'S COLUMN

## *The infant's love for his mother*

THE ORIGIN of the infant's love for his mother has been a subject for much speculation. A widely held view is that the infant learns to love his mother through the association of her face, body, and other physical characteristics with the satisfaction of hunger and thirst, a materialistic interpretation of human behavior. According to psychoanalytic theory the basis is the pleasure of attaining and sucking at the breast. Others hold that the infant's love for his mother is elicited by a variety of experiences which include nursing, physical contact, clinging, and even seeing and hearing.

The subject has been put to test by Harlow[1] in an ingenious series of experiments using newborn monkeys. His studies were designed to compare the importance of nursing and all associated activities with that of bodily contact in eliciting the infant's love for his mother. For this purpose two substitute "mothers" were constructed. One was a bare, welded-wire cylindrical form, surmounted by a crude wooden head and face; the other was similiar except that the wire was covered by a sheathing of terry cloth. Four newborn monkeys were assigned to each "mother"; they received their milk from a nursing bottle with its nipple protruding from the mother's "breast." Monkeys are much better suited for this type of study than is the human infant who is so immature at birth that he has little control over his motor apparatus, except for sucking. Moreover, motor maturation is so slow in the human infant that, by the time some degree of control has been attained, the nature of the mother-child relationship has been obscured by earlier experiences.

The two substitute mothers proved equally satisfactory nutritionally. Both groups of infant monkeys drank the same amount of milk and gained weight at the same rate. But they were by no means equally satisfied psychologically. Both groups of infants spent much more time climbing and clinging on the cloth-covered mother than they did on the wire mother, and the time spent in this way increased as they grew older.

The infants who secured their food from the wire mother remained with her no longer than feeding required. This observation is in direct contradiction of the view that affection is a response acquired from the association with the satisfaction of hunger or thirst.

Harlow's studies emphasize the importance of bodily contact and the immediate comfort which it supplies in forming the infant's attachment for its mother. He points out that in the natural nursing situation intimate bodily contact is effectively guaranteed. The mother who finds nursing a pleasant experience gives her baby plenty

of fondling. Comfort during contact is a decisive factor in the mother-child relationship.

Further information on the emotional attachment of the infant monkeys for their substitute mothers was obtained by observing their behavior under various stresses. When the infant monkeys were exposed to a mechanical teddy bear which moved forward beating a drum, they were terrified and rushed headlong for safety. Whether they had been suckled from the wire or the cloth mother they overwhelmingly rushed to the cloth one, clinging to her, and rubbing their bodies against hers. In the early experiments the terrified infant might rush to the wire mother, but he soon abandoned her for the cloth one. As experience grew he went directly to the cloth mother more and more.

After his fears were assuaged through contact with his mother, he would turn and look at the bear without the least sign of alarm and he might even leave the protection of the mother to explore the object which only a few minutes earlier had reduced him to terror.

Similiar results were obtained when the infant monkeys were exposed to other stressful situations, for example, a large room containing unfamiliar objects. Here again the infants rushed to the cloth mother, clinging to her, and rubbing against her. The wire mother provided no more reassurance than no mother at all.

In a further series of studies an experiment devised by Butler[2] was adopted. Butler had observed that monkeys enclosed in a dimly lighted box would press a lever to open and reopen a window again and again solely for the purpose of looking out. The rate at which they pressed the lever depended on what they saw through the open window. For example, the sight of another monkey elicited much more interest than a bowl of fruit or an empty room. This curiosity response is innate and already is evident in 3-day-old monkeys.

When the 2 groups of infant subjects were tested in a Butler box, the monkeys showed as high a response to the cloth mother as to another monkey. On the other hand, they displayed no more interest in the wire mother than in an empty room. Monkeys fed on the wire mother behaved like those fed on the cloth mother. A control group, raised with no mothers at all, found the cloth mother no more attractive than the wire mother and neither were as interesting as another monkey.

Harlow has sought to discover types of stimulation other than bodily contact that have to do with the development of infantile affection. One of these is rocking. When the infant monkeys were exposed to two cloth mother substitutes, one stationary, the other rocking, they preferred the rocking one. A rocking crib was preferred to a stationary one. The degree of preference varied from day to day and from monkey to monkey.

Warmth did not seem to affect the infant-mother relationship. Heating the substitute mother did not increase her attractiveness for the infant monkeys. The studies were made in a well-heated laboratory and different results might be obtained in a chillier atmosphere.

Harlow presents evidence that clinging itself may have some value in promoting psychological and physiologic well-being. Visual stimuli also enhance the attachment of the infant monkeys. At about 3 months they begin to explore the head, face, and eyes of their substitute mothers, a type of behavior seen somewhat later in human infants. It is of interest in this connection that, in the process of "imprinting," Lorenz[3] has found that the young of certain species of birds become attached to the first moving object, usually the mother.

In a further series of experiments 4 infant monkeys were denied any physical contact with a mother substitute or with other monkeys, thus simulating the situation where human infants are reared without affection. After about 8 months they were placed in cages with access to both cloth and wire mothers. At first they were timid but soon they began to respond much as

did the other infants, spending less than an hour a day on the wire mother and 8 to 10 hours on the cloth mother. This was, however, only about half the time spent on the cloth mother by infants raised with her from birth. Obviously, the "orphan" monkeys derived less comfort from the cloth mothers than did the "nonorphan" ones; the early deprivation had altered their capacity to develop a normal affectionate relationship.

To further study the effect of early deprivation, infant monkeys were separated from their cloth mothers at about 5½ months of age and then brought together again after about 18 months of separation. The infants showed little or no loss of responsiveness. By contrast, infant monkeys who had been introduced to a substitute mother only after the age of 8 months quickly lost whatever responsiveness they had acquired. Clearly the early period of maternal deprivation had altered permanently their capacity for forming a lasting affectionate relationship.

Harlow has devised an experimental approach for studying the subtle emotional relationships between mother and infant. His observations have already dissipated much that was speculative and misty.

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# *Comments on tropical pediatric literature: Bephenium in hookworm therapy*

THE prevention of the various helminthiases, which plays such an important part in the pathology of tropical children, rests ultimately with improving hygiene and sanitation, paralleled by higher standards of general and health education. In the meantime, the search continues for effective anthelminthics which can be used both in the therapy of clinical cases and also in attempts to control, or contain, this type of problem on a community basis by, for example, mass "deworming" of accessible groups of population, such as school children.

The hookworm is the intestinal helminth directly responsible for most deaths in childhood in tropical regions, as a result of anemia, due to the severe blood loss which may ensue with heavy worm burdens in poorly nourished and rapidly growing children. Therapy is therefore twofold—the hemoglobin has to be raised to safe levels and then the parasites removed, as far as possible, by chemotherapy.

Standard treatment of hookworm infection in most parts of the world is with tetrachlorethylene (0.1 ml. per kilogram of body weight), given as a single dose in a liquid form on an empty stomach. Experience in the Caribbean has shown that neither starvation nor purgation are needed at any stage.[1] The drug is very cheap, and, in the opinion of most, of low toxicity, although some workers prefer not to use it in grossly anemic children, with hemoglobin levels below 3 Gm. per 100 ml., until an initial transfusion of packed or sedimented red cells has been given cautiously. However, in tropical regions where facilities for blood transfusion do not exist, tetrachlorethylene has been used even in such exsanguinated pa-

tients. Nevertheless, as with all previous drugs employed, tetrachlorethylene is only partially effective against the hookworm, several repeated dosings at spaced intervals failing to eliminate all the parasites present; in addition, it has no effect against other helminths which may be present and, in particular, may sometimes stimulate roundworms to migrate, usually harmlessly but sometimes with ill effects, as when a bile duct may become blocked.

Bephenium compounds have been introduced recently to clinical pediatrics. The investigational background showed that various of these salts were active against *Ancylostoma caninum* in dogs and cats,[2] and of low toxicity and, ultimately, that less soluble compounds were poorly absorbed when given by mouth to human volunteers.[3]

Initial field trials were undertaken in Ceylon by Goodwin and associates[4] where they found that bephenium hydroxynaphthoate was probably the most suitable salt. A single dose of 2 to 3 Gm. of base, multiple doses given on successive days, or 3 times on the same day "compared favorably in effectiveness with tetrachlorethylene." No toxic side effects were observed even when large doses were given, and bephenium hydroxynaphthoate was found to be particularly suitable for the treatment of children with advanced anemia, diarrhea, and severe hookworm burdens. It was also considered to be effective against the roundworm.

During the past 18 months numerous trials of different levels of scientific quality and thoroughness have been, and are being, conducted in different parts of the world, and certain trends are becoming noticeable.

As bephenium hydroxynaphthoate (Alcopar) is sparingly soluble in water and only very little absorbed from the intestine when given orally, usual single dose regimens have been 2.5 Gm. ( 1 packet) of the drug for both adults and children over the age of 2 years and half this amount for younger children. The drug is usually given on an empty stomach, suspended in 1½ fluid ounces of water; no purgation is needed.

Results, in general, from all over the world seem to be falling into 2 general groups: those where single-dose therapy has been extremely effective and those where the drug has been valuable but removes only a lesser part of the worm burden. Among the former, investigations in West Pakistan,[5] rural Egypt,[6] and Léopoldville, Belgian Congo,[7] have shown substantial reductions in ova counts following treatment and apparent elimination of worms in the majority of subjects. Side effects were minimal, but most of these patients were adults. In the West Pakistan and Egyptian series, the hookworm was *Ancylostoma duodenale,* whereas the Congo cases were mostly infected with *Necator americanus.*

Results have been less striking elsewhere, including Kampala, Uganda, and possible explanations have to be considered. It may, for example, depend on the species of human hookworm—*A. duodenale* being much more sensitive than some strains of *N. americanus*—and this could be in accordance with the fact that in Uganda mixed infections are known to be common. Other factors which make comparative studies difficult, apart from variation in details of the regimen employed, are possibly the very different dietary habits in diverse tropical regions (probably with a variable intestinal bacterial flora), the varying age-incidence in different parts of the world (depending upon opportunities in the local ecology for skin contact with excreta-contaminated soil), and the inclusion in different series of variable proportions of asyptomatic hookworm infection and/or actual clinical disease. Finally, the problem is complicated by the difficulty both of assessing the hookworm burden initially and of gauging cure or improvement. The former is made difficult by the possibility of cyclical laying of eggs and also by the variable percentages present of male and female worms. "Cure" or improvement is also made more complex by the possibility that diminished or negative ova counts in the stools after therapy may be related to transient inhibition of laying of eggs rather than to the actual elimination of parasites.

As is always the way with new and potent drugs, a reassessment of dosage and precise regimen will have to be made in areas where present single-dose therapy has been found to be less effective than hoped. This can be attempted either by increasing the single dose or by giving the drug on more than one occasion.

The ideal anthelminthic for tropical children has yet to be found, and, indeed, may never be. Such a drug would have to be (1) effective in a single dose easily administered to young children as outpatients, without preparation or purgation, (2) nontoxic and with few side effects, (3) truly wide-spectrum helminthically, and (4) cheap.

Bephenium hydroxynaphthoate represents a useful additional drug for treating hookworm infection, and possibly other compounds of bephenium may be developed which will be more potent against apparently less sensitive strains of *N. americanus*. A particular advantage of bephenium hydroxynaphthoate, as compared with tetrachlorethylene, is its effect against the roundworm[4, 8] and, according to some, the whipworm. Pediatrically, apart from its apparent lesser efficacy against some strains of 1 of the 2 species of human hookworm, minor disadvantages are that it is sometimes difficult to persuade younger children to take the somewhat bitter suspension, so that administration via a polythene intragastric tube may be needed, while vomiting occasionally occurs. Possibly, and this is the crux of many problems of tropical pediatrics, economic considerations may well be paramount, since drugs employed on a widespread basis under present-day circumstances in relatively poor, technically developing countries have to be extremely inexpensive.

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# *The pediatrician and tuberculosis*

A RECENT study[1] by the U. S. Public Health Service has turned up some rather striking data on the risk of extrapulmonary complications of primary tuberculosis among tuberculin-positive infants and young children. This study was made in cooperation with 33 pediatric clinics throughout the United States as well as in Mexico City, San Juan, and Toronto, and involved 2,750 subjects.

It was clearly established that the risk of extrapulmonary complications is related to both age and extent of disease. Among infants less than 1 year of age who were

tuberculin reactors, without roentgen evidence of tuberculosis, the risk of extrapulmonary involvement within 2 years after diagnosis was 1 in 30. If there was roentgen evidence of hilar and/or paratracheal involvement, the risk increased to 1 in 8. When parenchymal involvement was observed, the risk was even higher, 1 in 6. On the other hand, for children from 1 to 4, the risk was substantial (1 in 26) only when there was roentgenographic involvement.

Fortunately, the study also established that the antituberculosis drug, isoniazid, can be expected to prevent 85 per cent of the progressive lesions that could otherwise be anticipated in infants and children in this age group. The Public Health Service,[2] on the basis of these findings, has recommended that all infants under 1 year of age who react to the tuberculin test and all children from 1 to 4 years of age who have, in addition, roentgen evidence of primary tuberculosis should be given 5 mg. of isoniazid per kilogram of body weight every day for 1 year.

In addition to practically eliminating the risk of extrapulmonary lesions among children with primary tuberculosis in these age groups, there is also some evidence that a year's prophylactic administration of isoniazid may also guard against reactivations in adolescence; the children in the study are still under observation to test this possibility.[2] Further evidence will be awaited with much interest since tuberculin-positive adolescents as a group have a high risk of developing tuberculosis.

The routine tuberculin testing of all infants and young children has been neglected recently, since in most areas the number of reactors is quite low and there was nothing that could be done to prevent the possible development of extrapulmonary lesions of primary tuberculosis. On the basis of this new knowledge, such testing has become distinctly worth while, and isoniazid prophylaxis for the reactors at high risk has become a necessity.

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